

**POLYCYCLIC  $\alpha$ -AMINO- $\epsilon$ -CAPROLACTAMS  
AND RELATED COMPOUNDS**

**CROSS-REFERENCE TO RELATED APPLICATIONS**

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A1  
This application is a Continuation-in-Part of U.S. Application No.  
09/337,408, filed May 11, 2001 which is a continuing prosecution application of  
U.S. Application No. 09/337,408 filed June 21, 1999 which claims the benefit of  
5 U.S. Provisional Application No. 60/160,066, filed June 22, 1998.

**BACKGROUND OF THE INVENTION**

1. Field of the Invention

10 This invention relates to polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactams and related  
compounds which are useful as synthetic intermediates in the preparation of  
inhibitors of  $\beta$ -amyloid peptide release and/or its synthesis.

2. References

15 The following publications, patents and patent applications are cited in  
this application as superscript numbers:

- 20 1 Glenner, et al., *Biochem. Biophys. Res. Commun.* (1984)  
120:885-890.
- 2 U.S. Patent No. 4,666,829, issued May 19, 1987, to G. G.  
Glenner et al., entitled "Polypeptide Marker for Alzheimer's  
Disease and Its Use for Diagnosis."
- 25 3 Selkoe, *Neuron.* (1991) 6:487-498.
- 4 Goate, et al., *Nature* (1990) 349:704-706.
- 5 Chartier Harlan, et al., *Nature* (1989) 353:844-846.
- 30 6 Murrell, et al., *Science* (1991) 254:97-99.

- 7 Mullan, et al., *Nature Genet.* (1992) 1:345-347.
- 8 T. W. Greene et al., *Protecting Groups in Organic Synthesis*,  
5 Second Edition, Wiley, New York (1991).
- 9 R. F. C. Brown et al., *Tetrahedron Letters* 1971, 8, 667-670.
- 10 A. O. King et al., *J. Org. Chem.* 1993, 58, 3384-3386.
- 11 *Tetrahedron Letters* 1993, 34(48), 7685.
- 12 U.S. Provisional Application Serial No. 60/019,790, filed June  
14, 1996.
- 13 U.S. Patent Application Serial No. 08/996,442, filed December  
15 19, 1997.
- 14 R. D. Clark et al., *Tetrahedron* 1993, 49(7), 1351-1356.
- 15 Schenk, et al., International Patent Application Publication No.  
20 WO 94/10569, "Methods and Compositions for the Detection of  
Soluble  $\beta$ -Amyloid Peptide", published 11 May 1994.
- 16 Citron, et al., *Nature* (1992) 360:672-674.
- 17 P. Seubert, *Nature* (1992) 359:325-327.
- 18 Hansen, et al., *J. Immun. Meth.*(1989) 119:203-210.
- 19 Games et al., *Nature* (1995) 373:523-527.
- 20 Johnson-Wood et al., *PNAS USA* (1997) 94:1550-1555.
- 35 All of the above publications, patents and patent applications are herein  
incorporated by reference in their entirety to the same extent as if each individual  
publication, patent or patent application was specifically and individually  
indicated to be incorporated by reference in its entirety.

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3. State of the Art

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently known.

The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type (HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other

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disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of about 39-43 amino acids designated the  $\beta$ -amyloid peptide ( $\beta$ AP) or sometimes  $A\beta$ ,  $A\beta P$  or  $\beta/A4$ .  $\beta$ -Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner, et al.<sup>1</sup> The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829<sup>2</sup>.

Molecular biological and protein chemical analyses have shown that the  $\beta$ -amyloid peptide is a small fragment of a much larger precursor protein termed the amyloid precursor protein (APP), that is normally produced by cells in many tissues of various animals, including humans. Knowledge of the structure of the gene encoding APP has demonstrated that  $\beta$ -amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). The precise biochemical mechanism by which the  $\beta$ -amyloid peptide fragment is cleaved from APP and subsequently deposited as amyloid plaques in the cerebral tissue and in the walls of the cerebral and meningeal blood vessels is currently unknown.

Several lines of evidence indicate that progressive cerebral deposition of  $\beta$ -amyloid peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe<sup>3</sup>. The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with a genetically determined (familial) form of AD (Goate, et al.<sup>4</sup>; Chartier Harlan, et al.<sup>5</sup>; and Murrell, et al.<sup>6</sup>) and is referred to as the Swedish variant. A double mutation changing lysine<sup>595</sup>-methionine<sup>596</sup> to asparagine<sup>595</sup>-leucine<sup>596</sup> (with reference to the 695 isoform) found in a Swedish family was reported in 1992 (Mullan, et al.<sup>7</sup>). Genetic linkage analyses have demonstrated that these mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a

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mutation at amino acid 693 of the 770-amino acid isoform of APP has been identified as the cause of the  $\beta$ -amyloid peptide deposition disease, HCHWA-D, and a change from alanine to glycine at amino acid 692 appears to cause a phenotype that resembles AD in some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP and subsequent deposition of its  $\beta$ -amyloid peptide fragment can cause AD.

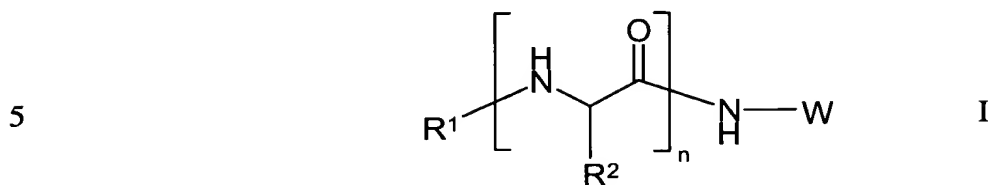
Despite the progress which has been made in understanding the underlying mechanisms of AD and other  $\beta$ -amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the disease(s). Ideally, the treatment methods would advantageously be based on drugs which are capable of inhibiting  $\beta$ -amyloid peptide release and/or its synthesis *in vivo*.

Compounds which inhibit  $\beta$ -amyloid peptide release and/or its synthesis *in vivo* are disclosed in U.S. Patent Application Serial No. 08/996,422, filed December 22, 1997 entitled "Cycloalkyl, Lactam, Lactone and Related Compounds, Pharmaceutical Compositions Comprising Same, and Methods for Inhibiting  $\beta$ -Amyloid Peptide Release, and/or its Synthesis by Use of Such Compounds," the disclosure of which is incorporated herein by reference in its entirety. The present invention is directed to intermediates useful in the preparation of such compounds.

## SUMMARY OF THE INVENTION

This invention is directed to the discovery of a class of intermediates which are useful in the preparation the cycloalkyl, lactam, lactone and related compounds described in U.S. Patent Application Serial No. 08/996,422, which compounds inhibit  $\beta$ -amyloid peptide release and/or its synthesis. Accordingly,

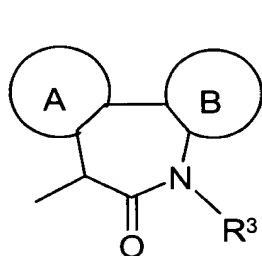
in one of its composition aspects, this invention is directed to a compound of formula I:



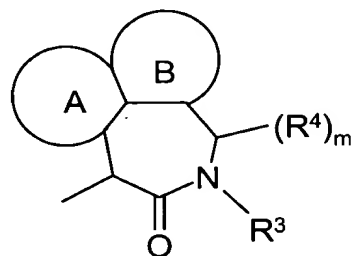
wherein

W is a substituted  $\epsilon$ -caprolactam selected from the group consisting of:

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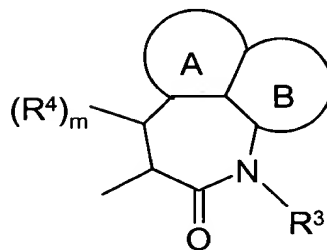


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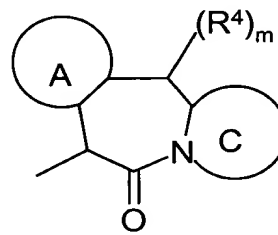


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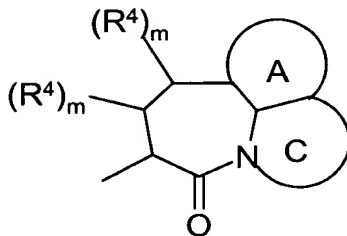


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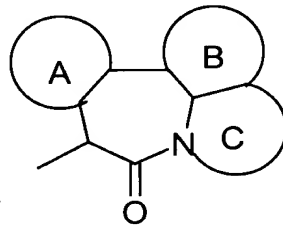


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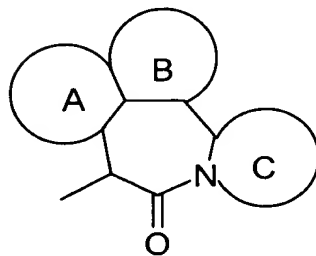


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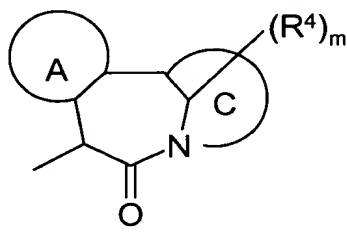


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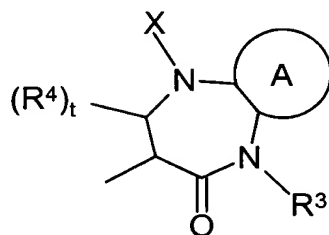
and



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or a substituted 1,5-diazepine of the formula:

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wherein

10 ring *A*, together with the atoms of the  $\epsilon$ -caprolactam or the substituted 1,5-diazepine to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

15 ring *B*, together with the atoms of the  $\epsilon$ -caprolactam to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

ring *C*, together with the atoms of the  $\epsilon$ -caprolactam to which it is attached, forms a heteroaryl or heterocyclic ring;

20  $R^1$  is selected from the group consisting of hydrogen and an amino-blocking group;

$R^2$  is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heteroaryl and heterocyclic;

25  $R^3$  is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

each  $R^4$  is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl,

cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

X is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic; or X and one of R<sup>4</sup> and the atoms to which they are attached form a double bond;

*m* is an integer from 0 to 2; *n* is 0 or 1; *t* is an integer from 0 to 2; and salts thereof.

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Preferably, R<sup>1</sup> is hydrogen, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), acetyl, 1-(1'-adamantyl)-1-methylethoxycarbonyl (Acm), allyloxycarbonyl (Aloc), benzyloxymethyl (Bom), 2-*p*-biphenylisopropylloxycarbonyl (Bpoc), *tert*-butyldimethylsilyl (Bsi), benzoyl (Bz), benzyl (Bn), 9-fluorenyl-methyloxycarbonyl (Fmoc), 4-methylbenzyl, 4-methoxybenzyl, 2-nitrophenylsulfenyl (Nps), 3-nitro-2-pyridinesulfenyl (NPys), trifluoroacetyl (Tfa), 2,4,6-trimethoxybenzyl (Tmob), trityl (Trt), and the like. More preferably, R<sup>1</sup> is hydrogen or *tert*-butoxycarbonyl (Boc).

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When *n* is one, R<sup>2</sup> is preferably selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic.

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Particularly preferred R<sup>2</sup> substituents include, by way of example, hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, -CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH<sub>2</sub>-cyclopropyl, -CH<sub>2</sub>-cyclohexyl, -CH<sub>2</sub>CH<sub>2</sub>-cyclopropyl, -CH<sub>2</sub>CH<sub>2</sub>-cyclohexyl, -CH<sub>2</sub>-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl,

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*m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH<sub>3</sub>)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O-benzyl, *p*-(CH<sub>3</sub>)<sub>3</sub>COC(O)CH<sub>2</sub>O-benzyl, *p*-(HOOCCH<sub>2</sub>O)-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH<sub>2</sub>CH<sub>2</sub>O)-benzyl, -CH<sub>2</sub>CH<sub>2</sub>C(O)NH<sub>2</sub>, -CH<sub>2</sub>-imidazol-4-yl, -CH<sub>2</sub>-(3-tetrahydrofuranyl), -CH<sub>2</sub>-thiophen-2-yl, -CH<sub>2</sub>(1-methyl)cyclopropyl, -CH<sub>2</sub>-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH<sub>2</sub>-C(O)O-*t*-butyl, -CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH<sub>3</sub>)<sub>2</sub>]COOCH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>, -CH<sub>2</sub>CH=CHCH<sub>3</sub> (cis and trans), -CH<sub>2</sub>OH, -CH(OH)CH<sub>3</sub>, -CH(O-*t*-butyl)CH<sub>3</sub>, -CH(O-CH<sub>2</sub>Ph)CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>NH-Boc, -(CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub>, -CH<sub>2</sub>-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH<sub>2</sub>-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH<sub>2</sub>-(4-morpholinyl), *p*-(4-morpholinyl-CH<sub>2</sub>CH<sub>2</sub>O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH<sub>2</sub>CH<sub>2</sub>SCH<sub>3</sub>, thien-2-yl, thien-3-yl, and the like.

Preferably, R<sup>3</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl and cycloalkyl.

Particularly preferred R<sup>3</sup> substituents include, by way of example, hydrogen, methyl, 2-methylpropyl, hexyl, methoxycarbonylmethyl, 3,3-dimethyl-2-oxobutyl, 4-phenylbutyl, cyclopropylmethyl, 2,2,2-trifluoroethyl, cyclohexyl, and the like.

When present, R<sup>4</sup> is preferably alkyl, substituted alkyl or aryl. When R is a substituted 1,5-diazepine, particularly preferred R<sup>4</sup> substituents include, by way of example, phenyl and isopropyl.

X is preferably hydrogen, alkyl or aryl; or X and one of R<sup>4</sup> and the atoms to which they are attached preferably form a double bond (i.e., -C(R<sup>4</sup>)=N-). Particularly preferred X substituents include, by way of example, methyl and phenyl.

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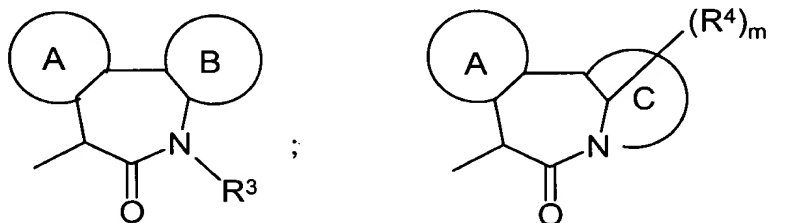
Preferably, *m* is 0 or 1. More preferably, *m* is 0.

Preferably, *t* is 0 or 1. In a preferred embodiment, *t* is 1.

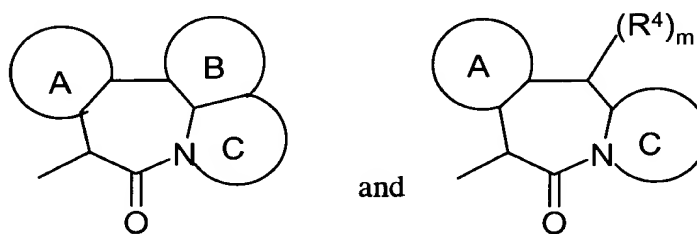
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W is preferably a substituted ε-caprolactam selected from the group consisting of:

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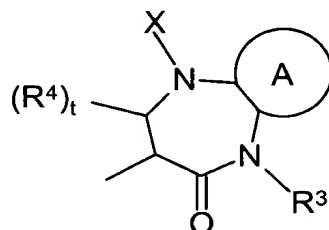


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or a substituted 1,5-diazepine of the formula:

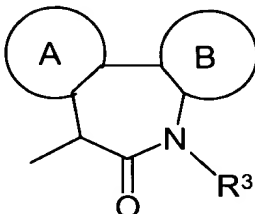
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wherein  $A$ ,  $B$ ,  $R^3$ ,  $R^4$ ,  $X$ ,  $m$  and  $t$  are as defined herein.

More preferably,  $W$  is a substituted  $\epsilon$ -caprolactam of the formula:



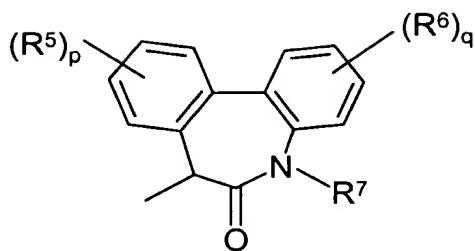
wherein  $A$ ,  $B$ , and  $R^3$  are as defined herein. In separate preferred embodiments, this invention is also directed to compounds of formula I wherein  $W$  is independently selected from each of the substituted  $\epsilon$ -caprolactams or the substituted 1,5-diazepin-2-one illustrated above.

Rings  $A$  and  $B$  may be the same or different and are preferably independently selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic. More preferably, rings  $A$  and  $B$  are independently selected from the group consisting of aryl and cycloalkyl. Still more preferably, rings  $A$  and  $B$  are independently aryl.

Particularly preferred  $A$  and  $B$  rings include, by way of example, phenyl, substituted phenyl, including fluoro-substituted phenyl, cyclohexyl and the like. When the  $A$  and  $B$  rings are fused to one another, they preferably form a naphthyl or substituted naphthyl ring.

Particularly preferred  $C$  rings include, by way of example, pyrrolidinyl, piperidinyl, morpholino and the like.

In one preferred embodiment of this invention,  $W$  is a substituted  $\epsilon$ -caprolactam of the formula:



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wherein

each  $R^5$  is independently selected from the group consisting of acyl,  
 10 acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy,  
 alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino,  
 aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted  
 cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted  
 thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl,  
 15 -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and  
 -SO<sub>2</sub>-heteroaryl;

each  $R^6$  is independently selected from the group consisting of acyl,  
 acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy,  
 alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino,  
 20 aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted  
 cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted  
 thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl,  
 -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and  
 -SO<sub>2</sub>-heteroaryl;

25  $R^7$  is selected from the group consisting of hydrogen, alkyl, substituted  
 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl,  
 cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl,  
 heteroaryl and heterocyclic;

$p$  is an integer from 0 to 4;  $q$  is an integer from 0 to 4; and salts thereof.

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Preferably,  $R^5$  and  $R^6$  are independently selected from the group consisting of alkoxy, substituted alkoxy, alkyl, substituted alkyl, amino, substituted amino, carboxyl, carboxyalkyl, cyano, halo, nitro, thioalkoxy and substituted thioalkoxy. More preferably, when present,  $R^5$  and  $R^6$  are fluoro.

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$R^7$  is preferably selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, aryl, cycloalkyl and substituted cycloalkyl. More preferably,  $R^7$  is selected from the group consisting of hydrogen, alkyl, substituted alkyl and cycloalkyl.

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Particularly preferred  $R^7$  substituents include, by way of example, hydrogen, methyl, 2-methypropyl, hexyl, methoxycarbonylmethyl, 3,3-dimethyl-2-oxobutyl, 4-phenylbutyl, cyclopropylmethyl, 2,2,2-trifluoroethyl, cyclohexyl, and the like.

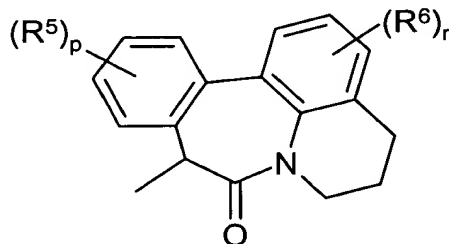
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In a preferred embodiment,  $n$  is 0;  $p$ ,  $q$  and  $r$  are independently 0, 1 or 2; each  $R^5$  in the above formula is independently selected from the group consisting of alkyl, substituted alkyl, alkoxy, and halo; each  $R^6$  is independently selected from the group consisting of alkyl, substituted alkyl, alkoxy, and halo; and each  $R^7$  is independently selected from the group consisting of alkyl, substituted alkyl, cycloalkyl and aryl. Preferably,  $p$  and  $q$  are independently 0 or 1.

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In another preferred embodiment of this invention,  $W$  is a substituted  $\epsilon$ -caprolactam of the formula:

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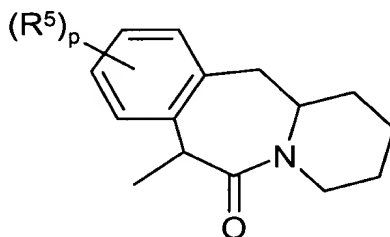
wherein  $R^5$ ,  $R^6$ , and  $p$  are as defined herein and  $r$  is an integer from 0 to 3; and salts thereof.

5            In a preferred embodiment,  $n$  is 0;  $p$  and  $r$  are independently 0, 1 or 2; each  $R^5$  in the above formula is independently selected from the group consisting of alkyl, substituted alkyl, alkoxy, and halo; and each  $R^6$  is independently selected from the group consisting of alkyl, substituted alkyl, alkoxy, and halo. Preferably,  $p$  and  $r$  are independently 0 or 1.

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          In still another preferred embodiment of this invention,  $W$  is a substituted  $\epsilon$ -caprolactam of the formula:

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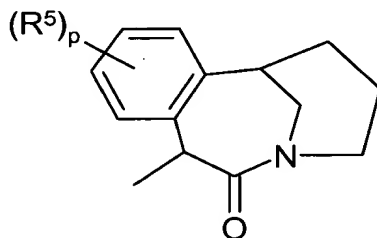


wherein  $R^5$ , and  $p$  are as defined herein; and salts thereof.

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          In yet another preferred embodiment of this invention,  $W$  is a substituted  $\epsilon$ -caprolactam of the formula:

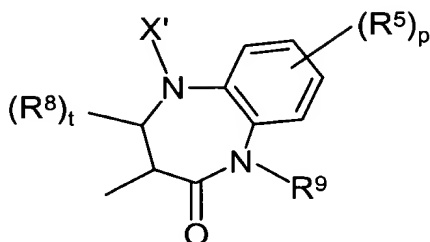
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wherein  $R^5$  and  $p$  are as defined herein; and salts thereof.

In still another preferred embodiment of this invention, *W* is a 1,5-benzodiazepine of the formula:



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where  $R^5$ ,  $p$  and  $t$  are as defined herein; each  $R^8$  is independently selected from the group consisting of alkyl, heterocyclic and aryl;  $R^9$  is alkyl; and  $X'$  is selected from the group consisting of hydrogen, alkyl and aryl; or  $X'$  and one of  $R^8$  and the atoms to which they are attached form a double bond.

15

Preferably,  $R^8$  is alkyl or aryl. More preferably,  $R^8$  is isopropyl or phenyl.

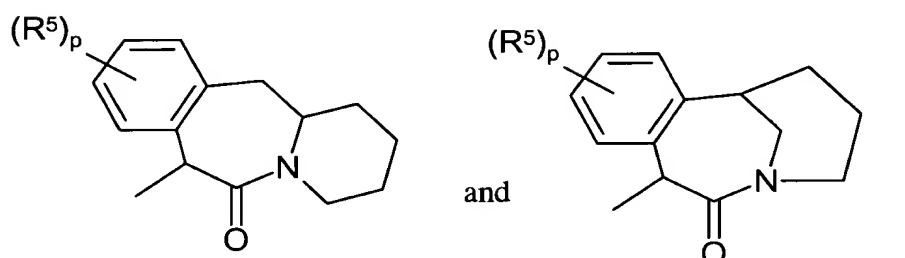
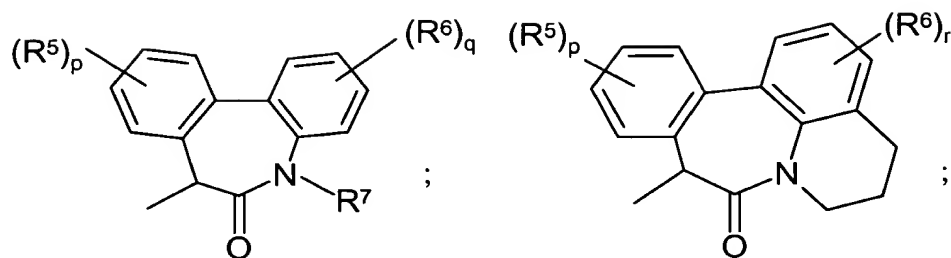
20

$X'$  is preferably hydrogen, methyl or phenyl; or  $X'$  and one of  $R^8$  and the atoms to which they are attached preferably form a double bond.

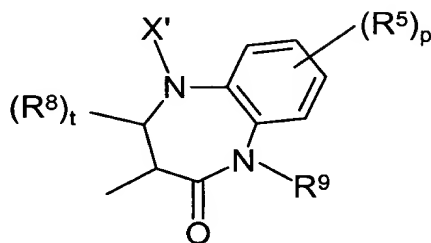
25

When  $n$  is 1, *W* is preferably a substituted  $\epsilon$ -caprolactam selected from the group consisting of:

30



or a 1,5-benzodiazepine of the formula:



20 wherein  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $X'$ ,  $m$ ,  $p$ ,  $q$ ,  $r$  and  $t$  are as defined herein.  
 Preferably, in this embodiment,  $p$ ,  $q$  and  $r$  are independently 0 or 1; each  $R^5$  is  
 independently selected from the group consisting of alkyl, substituted alkyl,  
 cycloalkyl, alkoxy, and halo; each  $R^6$  is independently selected from the group  
 consisting of alkyl, substituted alkyl, cycloalkyl, alkoxy, and halo; and each  $R^7$  is  
 25 independently selected from the group consisting of alkyl, substituted alkyl,  
 cycloalkyl and aryl. More preferably,  $p$ ,  $q$  and  $r$  are 0.

Preferred substituted  $\epsilon$ -caprolactams (i.e.,  $W$ ) include, by way of  
 example, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-methyl-5,7-dihydro-  
 30 6H-dibenz[b,d]azepin-6-one-5-yl, 7-(2-methylpropyl)-5,7-dihydro-6H-



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dibenz[b,d]azepin-6-one-5-yl, 7-(methoxyacetyl)-5,7-dihydro-6H-  
dibenz[b,d]azepin-6-one-5-yl, 7-(3,3-dimethylbutan-2-onyl)-5,7-dihydro-6H-  
dibenz[b,d]azepin-6-one-yl, 7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-  
one-yl, 7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-  
5 (2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-  
cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-hexyl-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one-5-yl, 9-fluoro-7-methyl-5,7-dihydro-6H-  
dibenz[b,d]azepin-6-one-5-yl, 10-fluoro-7-methyl-5,7-dihydro-6H-  
dibenz[b,d]azepin-6-one-5-yl, 13-fluoro-7-methyl-5,7-dihydro-6H-  
10 dibenz[b,d]azepin-6-one-5-yl and 7-methyl-1,2,3,4,5,7-hexahydro-6H-  
dicyclohexyl[b,d]azepin-6-one-5-yl.

Preferred substituted 1,5-diazepines include, by way of illustration, 1,3-  
dihydro-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one-3-yl, 1,3,4,5-  
15 tetrahydro-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one-3-yl, 1,3-dihydro-1-  
methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one-3-yl, 1,3,4,5-tetrahydro-1-  
methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one-3-yl, 1-methyl-5-phenyl-  
1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one-3-yl and 1,5-bis-methyl-  
1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one-3-yl.

20

Compounds of this invention include, by way of example, the following:

5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(*N*-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25

5-(*N*-Boc-amino)-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-  
6-one

5-amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

30

5-(*N*-Boc-amino)-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-  
dibenz[b,d]azepin-6-one

5-amino-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-  
one

35

5-(*N*-Boc-amino)-7-(3,3-dimethyl-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-amino-7-(3,3-dimethyl-2-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

**5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

5-amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25 5-amino-7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one

5-(*N*-Boc-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[*b,d*]azepin-6-one

30 5-(L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

**5-(*N*-Boc-L-valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[*b,d*]azepin-6-one**

35 5-(L-valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(*N*-Boc-L-*tert*-leucinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[*b,d*]azepin-6-one

40 5-(L-*tert*-leucinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(*N*-Boc-L-alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[*b,d*]azepin-6-one

45

- 5-(L-alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-(*N*-Boc-L-alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-(L-alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-(L-alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-(*N*-Boc-L-alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-(L-alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-(*N*-Boc-L-alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-(L-alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-(*N*-Boc-L-valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-(L-valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

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- 5-(L-valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-(N-Boc-L-valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-(L-valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-(N-Boc-L-valinyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-9,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-amino-10,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-9,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-10,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-amino-9,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 9-amino-5,6-Dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one
- 9-(N'-Boc-L-alaninyl)amino-5,6-Dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one
- 30 9-(N'-L-alaninyl)amino-5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one
- 7-amino-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one
- 1-amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- 35 1-(N'-Boc-L-alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- 1-(N'-L-alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- 40 and salts thereof.
- 45

Additional compounds of this invention include, by way of example, the following:

- 5 1,3-dihydro-3-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one
- 1,3-dihydro-3-(N-Boc-L-alaninyl)amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one
- 10 1,3-dihydro-3-(L-alaninyl)amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one
- 1,3,4,5-tetrahydro-3-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one
- 15 1,3,4,5-tetrahydro-3-(N-Boc-L-alaninyl)amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one
- 1,3,4,5-tetrahydro-3-(L-alaninyl)amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one
- 20 1,3-dihydro-3-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 1,3-dihydro-3-(N-Boc-L-alaninyl)amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 25 1,3-dihydro-3-(L-alaninyl)amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 1,3,4,5-tetrahydro-3-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 30 1,3,4,5-tetrahydro-3-(N-Boc-L-alaninyl)amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 1,3,4,5-tetrahydro-3-(L-alaninyl)amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 35 1,3-dihydro-3-(N-Boc-L-norleucinyl)amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 1,3-dihydro-3-(L-norleucinyl)amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 40 1,3,4,5-tetrahydro-3-(N-Boc-L-norleucinyl)amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one
- 45

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- 1,3,4,5-tetrahydro-3-(L-norleucinyl)amino-1-methyl-4-isopropyl-(2H)-  
1,5-benzodiazepin-2-one
- 5 1,3-dihydro-3-(N-Boc-L-norleucinyl)amino-1-methyl-4-phenyl-(2H)-1,5-  
benzodiazepin-2-one
- 1,3-dihydro-3-(L-norleucinyl)amino-1-methyl-4-phenyl-(2H)-1,5-  
benzodiazepin-2-one
- 10 3-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-  
one
- 3-(N-Boc-L-alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-  
1,5-benzodiazepine-2-one
- 15 3-(L-alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-  
benzodiazepine-2-one
- 3-(N-Boc-L-valinyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-  
1,5-benzodiazepin-2-one
- 20 3-(L-valinyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-  
benzodiazepin-2-one
- 25 3-[N-Boc-L-(O-benzyl)-threoninyl]amino-1-methyl-5-phenyl-1,3,4,5-  
tetrahydro-(2H)-1,5-benzodiazepin-2-one
- 3-[L-(O-benzyl)-threoninyl]amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-  
(2H)-1,5-benzodiazepin-2-one
- 30 3-[N-Boc-(S)-phenylglycinyl]amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-  
(2H)-1,5-benzodiazepine 2-one
- 35 3-[(S)-phenylglycinyl]amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-  
1,5-benzodiazepine 2-one
- 3-amino-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one
- 3-(N-Boc-L-alaninyl)amino-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-  
benzadiazepine-2-one
- 40 3-(L-alaninyl)amino-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-  
benzadiazepine-2-one
- 45 and salts thereof.

In one embodiment, the following compounds are not preferred:

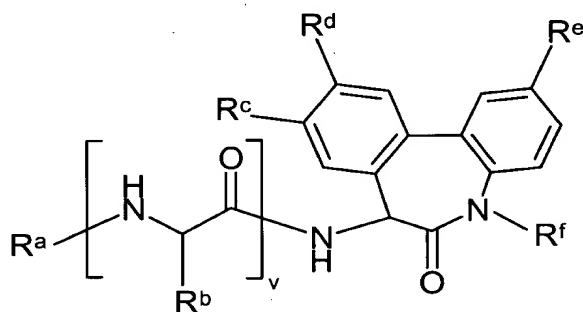
3-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one

5 3-(N-Boc-L-alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one, and

10 3-(L-alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one.

Preferred compounds include those defined by the formulas as set forth in the following Tables and salts thereof.

Table I



15	$R^a$	$R^b$	$R^c$	$R^d$	$R^e$	$R^f$	$v$
	H-	---	H-	H-	H-	$CH_3-$	0
	Boc- <sup>a</sup>	---	H-	H-	H-	H-	0
	Boc-	---	H-	H-	H-	$(CH_3)_2CHCH_2-$	0
	H-	---	H-	H-	H-	$(CH_3)_2CHCH_2-$	0
20	Boc-	---	H-	H-	H-	$CH_3OC(O)CH_2-$	0
	H-	---	H-	H-	H-	$CH_3OC(O)CH_2-$	0
	Boc-	---	H-	H-	H-	$(CH_3)_3CC(O)CH_2-$	0
	H-	---	H-	H-	H-	$(CH_3)_3CC(O)CH_2-$	0
	H-	---	H-	H-	H-	$Ph(CH_2)_4-$	0
25	H-	---	H-	H-	H-	cyclopropyl- $CH_2-$	0

	R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>	R <sup>d</sup>	R <sup>e</sup>	R <sup>f</sup>	$\nu$
5	H-	---	H-	H-	H-	CF <sub>3</sub> CH <sub>2</sub> -	0
	H-	---	H-	H-	H-	cyclohexyl-	0
	H-	---	H-	H-	H-	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> -	0
	H-	---	F-	H-	H-	CH <sub>3</sub> -	0
	H-	---	H-	F-	H-	CH <sub>3</sub> -	0
	H-	---	H-	H-	F-	CH <sub>3</sub> -	0
10	Boc-	CH <sub>3</sub> -	H-	H-	H-	CH <sub>3</sub> -	1
	H-	CH <sub>3</sub> -	H-	H-	H-	CH <sub>3</sub> -	1
	Boc-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	CH <sub>3</sub> -	1
	H-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	CH <sub>3</sub> -	1
	Boc-	(CH <sub>3</sub> ) <sub>3</sub> C-	H-	H-	H-	CH <sub>3</sub> -	1
	H-	(CH <sub>3</sub> ) <sub>3</sub> C-	H-	H-	H-	CH <sub>3</sub> -	1
15	Boc-	CH <sub>3</sub> -	F-	H-	H-	CH <sub>3</sub> -	1
	H-	CH <sub>3</sub> -	F-	H-	H-	CH <sub>3</sub> -	1
	Boc-	CH <sub>3</sub> -	H-	F-	H-	CH <sub>3</sub> -	1
	H-	CH <sub>3</sub> -	H-	F-	H-	CH <sub>3</sub> -	1
	Boc-	CH <sub>3</sub> -	H-	H-	F-	CH <sub>3</sub> -	1
	H-	CH <sub>3</sub> -	H-	H-	F-	CH <sub>3</sub> -	1
20	Boc-	CH <sub>3</sub> -	H-	H-	H-	cyclopropyl-CH <sub>2</sub> -	1
	H-	CH <sub>3</sub> -	H-	H-	H-	cyclopropyl-CH <sub>2</sub> -	1
	Boc-	CH <sub>3</sub> -	H-	H-	H-	Ph(CH <sub>2</sub> ) <sub>4</sub> -	1
	H-	CH <sub>3</sub> -	H-	H-	H-	Ph(CH <sub>2</sub> ) <sub>4</sub> -	1
	Boc-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	cyclopropyl-CH <sub>2</sub> -	1
	H-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	cyclopropyl-CH <sub>2</sub> -	1
25	Boc-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	Ph(CH <sub>2</sub> ) <sub>4</sub> -	1
	H-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	Ph(CH <sub>2</sub> ) <sub>4</sub> -	1
	Boc-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> -	1

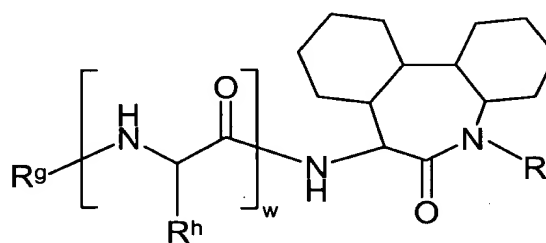
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R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>	R <sup>d</sup>	R <sup>e</sup>	R <sup>f</sup>	v
H-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	H-	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> -	1
Boc-	(CH <sub>3</sub> ) <sub>2</sub> CH-	F-	H-	H-	CH <sub>3</sub> -	1
H-	(CH <sub>3</sub> ) <sub>2</sub> CH-	F-	H-	H-	CH <sub>3</sub> -	1
Boc-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	F-	H-	CH <sub>3</sub> -	1
H-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	F-	H-	CH <sub>3</sub> -	1
Boc-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	F-	CH <sub>3</sub> -	1
H-	(CH <sub>3</sub> ) <sub>2</sub> CH-	H-	H-	F-	CH <sub>3</sub> -	1
H-	---	F-	H-	F-	CH <sub>3</sub> -	0
H-	---	H-	F-	F-	CH <sub>3</sub> -	0

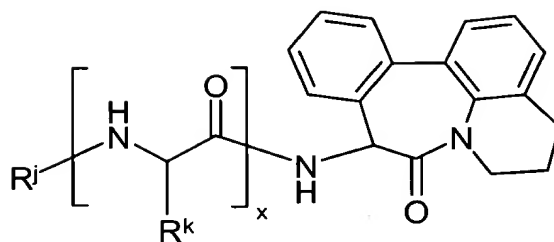
<sup>a</sup> Boc = *tert*-butoxycarbonyl = (CH<sub>3</sub>)<sub>3</sub>COC(O)-

Table II



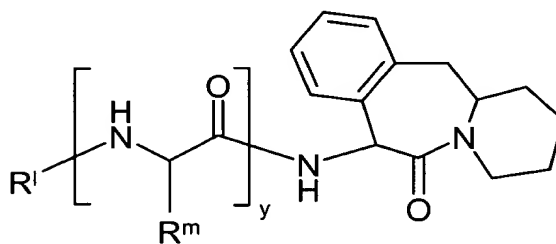
R <sup>g</sup>	R <sup>h</sup>	R <sup>i</sup>	w
H-	---	CH <sub>3</sub> -	0

Table III



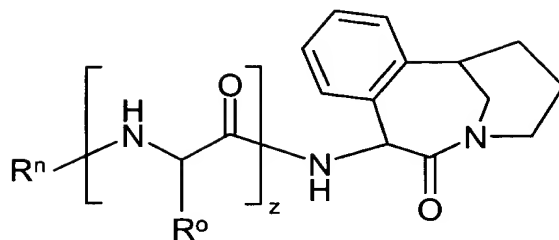
$R^j$	$R^k$	$x$
H-	---	0
H-	CH <sub>3</sub> -	1

Table IV



$R^l$	$R^m$	$y$
H-	---	0

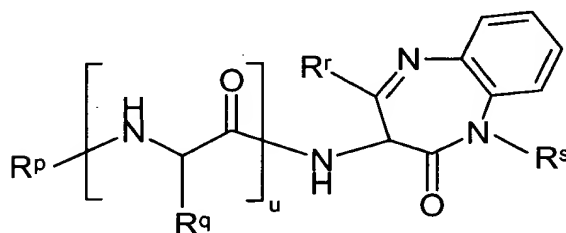
Table V



$R^n$	$R^o$	$z$
H-	---	0
Boc- <sup>a</sup>	CH <sub>3</sub> -	1
H-	CH <sub>3</sub> -	1

<sup>a</sup> Boc = *tert*-butoxycarbonyl = (CH<sub>3</sub>)<sub>3</sub>COC(O)-

Table VI

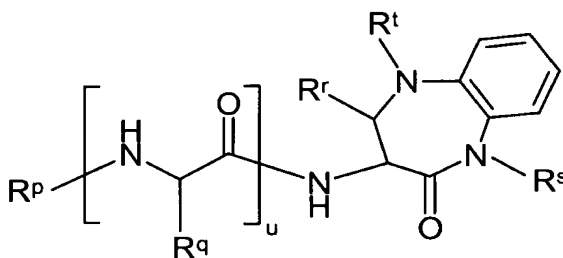


$R^p$	$R^q$	$R^r$	$R^s$	$u$
H-	---	-Ph	-CH <sub>3</sub>	0
H-	---	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	0
Boc- <sup>a</sup>	-CH <sub>3</sub>	-Ph	-CH <sub>3</sub>	1

R <sup>p</sup>	R <sup>q</sup>	R <sup>r</sup>	R <sup>s</sup>	u
H-	-CH <sub>3</sub>	-Ph	-CH <sub>3</sub>	1
Boc-	-CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	1
H-	-CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	1
Boc-	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	1
H-	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	1
Boc-	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	-Ph	-CH <sub>3</sub>	1
H-	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	-Ph	-CH <sub>3</sub>	1

<sup>a</sup> Boc = *tert*-butoxycarbonyl = (CH<sub>3</sub>)<sub>3</sub>COC(O)-

Table VII



R <sup>p</sup>	R <sup>q</sup>	R <sup>r</sup>	R <sup>s</sup>	R <sup>t</sup>	u
H-	---	-Ph	-CH <sub>3</sub>	-H	0
H-	---	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	-H	0
Boc- <sup>a</sup>	-CH <sub>3</sub>	-Ph	-CH <sub>3</sub>	-H	1
H-	-CH <sub>3</sub>	-Ph	-CH <sub>3</sub>	-H	1
Boc-	-CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	-H	1
H-	-CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	-H	1

5

10

15

R <sup>p</sup>	R <sup>q</sup>	R <sup>r</sup>	R <sup>s</sup>	R <sup>t</sup>	u
Boc-	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	-H	1
H-	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	-H	1
H-	---	-H	-CH <sub>3</sub>	-Ph	0
Boc-	-CH <sub>3</sub>	-H	-CH <sub>3</sub>	-Ph	1
H-	-CH <sub>3</sub>	-H	-CH <sub>3</sub>	-Ph	1
Boc-	-CH(CH <sub>3</sub> ) <sub>2</sub>	-H	-CH <sub>3</sub>	-Ph	1
H-	-CH(CH <sub>3</sub> ) <sub>2</sub>	-H	-CH <sub>3</sub>	-Ph	1
Boc-	-CH(CH <sub>3</sub> )OCH <sub>2</sub> -Ph	-H	-CH <sub>3</sub>	-Ph	1
H-	-CH(CH <sub>3</sub> )OCH <sub>2</sub> -Ph	-H	-CH <sub>3</sub>	-Ph	1
Boc-	-Ph	-H	-CH <sub>3</sub>	-Ph	1
H-	-Ph	-H	-CH <sub>3</sub>	-Ph	1
H-	---	-H	-CH <sub>3</sub>	-CH <sub>3</sub>	
Boc-	-CH <sub>3</sub>	-H	-CH <sub>3</sub>	-CH <sub>3</sub>	1
H-	-CH <sub>3</sub>	-H	-CH <sub>3</sub>	-CH <sub>3</sub>	1

<sup>a</sup> Boc = *tert*-butoxycarbonyl = (CH<sub>3</sub>)<sub>3</sub>COC(O)-

## DETAILED DESCRIPTION OF THE INVENTION

20

For purposes of describing this invention in all its aspects, the following terms have the followings meanings unless otherwise indicated. All other terms have their conventional art-recognized meanings.

### Definitions

25

The term "β-amyloid peptide" refers to a 39-43 amino acid peptide having a molecular weight of about 4.2 kD, which peptide is substantially homologous to the form of the protein described by Glenner, et al.<sup>1</sup> including mutations and post-translational modifications of the normal β-amyloid peptide. In whatever

form, the  $\beta$ -amyloid peptide is an approximate 39-43 amino acid fragment of a large membrane-spanning glycoprotein, referred to as the  $\beta$ -amyloid precursor protein (APP). Its 43-amino acid sequence is:

5     1  
Asp Ala Glu Phe Arg His Asp Ser Gly Tyr

11  
10   Glu Val His His Gln Lys Leu Val Phe Phe

21  
Ala Glu Asp Val Gly Ser Asn Lys Gly Ala

31  
15   Ile Ile Gly Leu Met Val Gly Gly Val Val

41  
Ile Ala Thr (SEQ ID NO: 1)

20   or a sequence which is substantially homologous thereto.

"Alkyl" refers to monovalent alkyl groups preferably having from 1 to 20 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified  
25   by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, decyl and the like.

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 20 carbon atoms, having from 1 to 5 substituents, and preferably 1 to 3 substituents,  
30   selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy,  
35   heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -

SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl.

5 "Alkylene" refers to divalent alkylene groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), the propylene isomers (e.g., -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH(CH<sub>3</sub>)CH<sub>2</sub>-) and the like.

10 "Substituted alkylene" refers to an alkylene group, preferably of from 1 to 10 carbon atoms, having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, 15 aryl, heteroaryl, heterocyclic, heterocycloxy, nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. 20 Preferably such fused cycloalkyl groups contain from 1 to 3 fused ring structures.

"Alkenylene" refers to divalent alkenylene groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms. This term is 25 exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., -CH<sub>2</sub>CH=CH- and -C(CH<sub>3</sub>)=CH-) and the like.

"Substituted alkenylene" refers to an alkenylene group, preferably of from 2 to 10 carbon atoms, having from 1 to 3 substituents selected from the group 30 consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl,

cycloalkoxy, substituted cycloalkoxyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, heterocycloxy, nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group.

10 "Alkaryl" refers to -alkylene-aryl groups preferably having from 1 to 8 carbon atoms in the alkylene moiety and from 6 to 10 carbon atoms in the aryl moiety. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

15 "Alkoxy" refers to the group "alkyl-O-". Preferred alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

20 "Substituted alkoxy" refers to the group "substituted alkyl-O-" where substituted alkyl is as defined above.

25 "Alkylalkoxy" refers to the group "-alkylene-O-alkyl" which includes by way of example, methylenemethoxy (-CH<sub>2</sub>OCH<sub>3</sub>), ethylenemethoxy (-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>), *n*-propylene-*iso*-propoxy (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>), methylene-*t*-butoxy (-CH<sub>2</sub>-O-C(CH<sub>3</sub>)<sub>3</sub>) and the like.

30 "Alkylthioalkoxy" refers to the group "-alkylene-S-alkyl" which includes by way of example, methylenethiomethoxy (-CH<sub>2</sub>SCH<sub>3</sub>), ethylenethiomethoxy (-CH<sub>2</sub>CH<sub>2</sub>SCH<sub>3</sub>), *n*-propylene-thio-*iso*-propoxy (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SCH(CH<sub>3</sub>)<sub>2</sub>), methylenethio-*t*-butoxy (-CH<sub>2</sub>SC(CH<sub>3</sub>)<sub>3</sub>) and the like.



"Alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl ( $-\text{CH}=\text{CH}_2$ ), *n*-propenyl ( $-\text{CH}_2\text{CH}=\text{CH}_2$ ), *iso*-propenyl ( $-\text{C}(\text{CH}_3)=\text{CH}_2$ ), and the like.

"Substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, heterocycloxy, nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl.

"Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation. Preferred alkynyl groups include ethynyl ( $-\text{C}\equiv\text{CH}$ ), propargyl ( $-\text{CH}_2\text{C}\equiv\text{CH}$ ) and the like.

"Substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, heterocycloxy, nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl.

"Acyl" refers to the groups alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

5

"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic and where both R groups are joined to form a heterocyclic group, wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

10

"Amino" refers to the group -NH<sub>2</sub>.

"Substituted amino" refers to the group -N(R)<sub>2</sub> where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, heterocyclic and where both R groups are joined to form a heterocyclic group. When both R groups are hydrogen, -N(R)<sub>2</sub> is an amino group. Examples of substituted amino groups include, by way of illustration, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic, and the like.

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The term "amino-blocking group" or "amino-protecting group" refers to any group which, when bound to an amino group, prevents undesired reactions from occurring at the amino group and which may be removed by conventional chemical and/or enzymatic procedures to reestablish the amino group. Any known amino-blocking group may be used in this invention. Typically, the

30

amino-blocking group is selected so as to render the resulting blocked-amino group unreactive to the particular reagents and reaction conditions employed in a subsequent pre-determined chemical reaction or series of reactions. After completion of the reaction(s), the amino-blocking group is selectively removed to regenerate the amino group. Examples of suitable amino-blocking groups include, by way of illustration, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), acetyl, 1-(1'-adamantyl)-1-methylethoxycarbonyl (Acm), allyloxycarbonyl (Aloc), benzyloxymethyl (Bom), 2-*p*-biphenylisopropylloxycarbonyl (Bpoc), *tert*-butyldimethylsilyl (Bsi), benzoyl (Bz), benzyl (Bn), 9-fluorenyl-methyloxycarbonyl (Fmoc), 4-methylbenzyl, 4-methoxybenzyl, 2-nitrophenylsulfenyl (Nps), 3-nitro-2-pyridinesulfenyl (NPys), trifluoroacetyl (Tfa), 2,4,6-trimethoxybenzyl (Tmob), trityl (Trt), and the like. If desired, amino-blocking groups covalently attached to a solid support may also be employed.

"Aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Aminoacyloxy" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

5

Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heterocyclic, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl and trihalomethyl. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

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"Aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

20

"Carboxyalkyl" refers to the groups "-C(O)Oalkyl" and "-C(O)O-substituted alkyl" where alkyl is as defined above.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 12 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

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"Substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 (preferably 1 to 3) substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 8 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

"Substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either fluoro or chloro.

"Heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

- 5 Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, substituted amino, aminoacyl, acylamino, 10 alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heterocyclic, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl and trihalomethyl. Such heteroaryl groups can have a single ring 15 (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indoliziny1 or benzothieryl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

"Heteroaryloxy" refers to the group "-O-heteroaryl".

- 20 "Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 15 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or oxygen within the ring.

- 25 Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, 30 oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto,

thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, and -SO<sub>2</sub>-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of heterocycles and heteroaryls include, but are not limited to, pyrrole, furan, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

"Heterocyclooxy" refers to the group "-O-heterocycle".

"Keto" or "oxo" refers to the group "=O".

"Oxyacylamino" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Thiol" refers to the group -SH.

"Thioalkoxy" refers to the group -S-alkyl.

"Substituted thioalkoxy" refers to the group -S-substituted alkyl.

"Thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

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"Thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

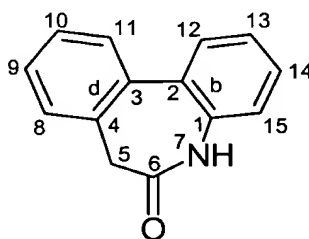
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"Thioketo" refers to the group "=S".

As to any of the above defined groups which contain 1 or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

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The term "5,7-dihydro-6H-dibenz[b,d]azepin-6-one" refers to a polycyclic  $\epsilon$ -caprolactam ring system having the formula:

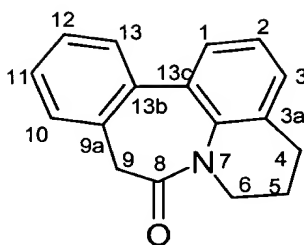


wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

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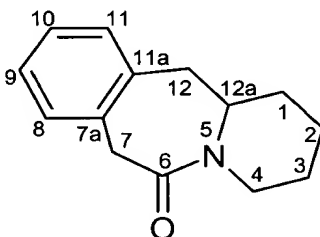
The term "5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one" refers to a polycyclic  $\epsilon$ -caprolactam ring system having the formula:





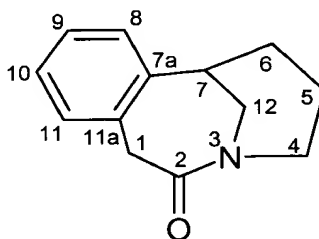
wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

5 The term "1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one" refers to a polycyclic  $\epsilon$ -caprolactam ring system having the formula:



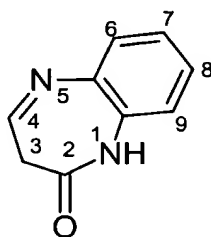
wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

10 The term "4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one" refers to a polycyclic  $\epsilon$ -caprolactam ring system having the formula:



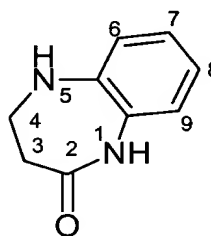
wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

The term "1,3-dihydro-(2H)-1,5-benzodiazepin-2-one" refers to a ring system having the formula:



wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

The term "1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one" refers to a ring system having the formula:



wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

The term "salt(s)" refers to salts of a compound of formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the

molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

5           The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, carboxyl or other protectable functional group of the compound prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical and/or enzymatic steps to reestablish the unprotected functional group. The  
10       particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzyldiene, phenacyl, *tert*-butyldiphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or  
15       enzymatic methods in mild conditions compatible with the nature of the product.

          Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *tert*-butyl, etc. which can be removed by mild hydrolysis conditions compatible with the nature of the product.

20

#### Compound Preparation

          The polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactams and related compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where  
25       typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

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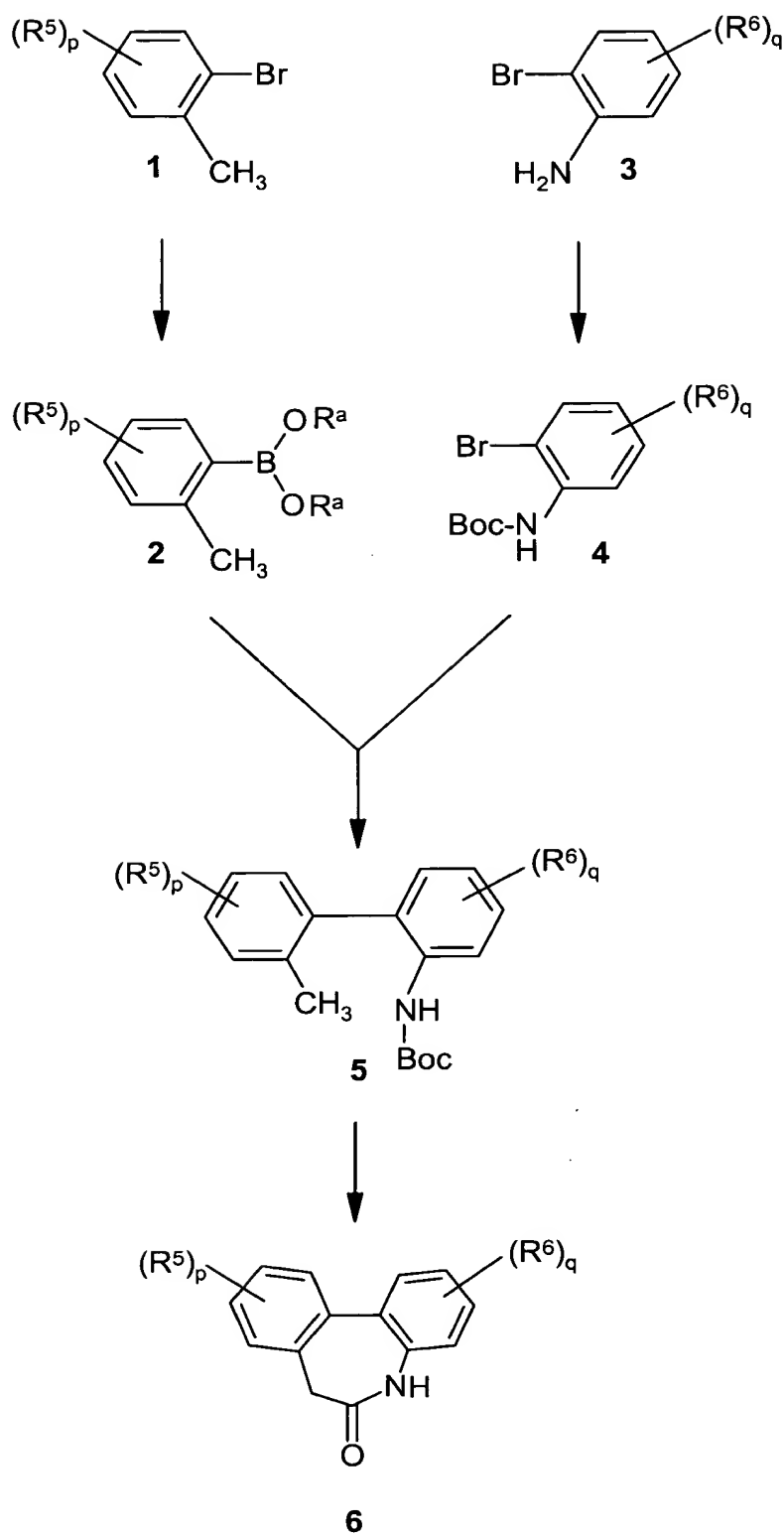
Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991,<sup>8</sup> and references cited therein.

In a preferred method of synthesis, the  $\epsilon$ -caprolactams of this invention are prepared by first aminating a polycyclic  $\epsilon$ -caprolactam to provide a polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactam. If desired, the amino group of the polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactam can then be coupled with a mono- or diamino acid derivative to provide compounds of formula I wherein  $n$  is 1.

The polycyclic  $\epsilon$ -caprolactams employed as starting materials in this invention are either commercially available or can be prepared from commercially available materials using conventional procedures and reagents. For example, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one may be prepared by cyclizing a chloromethyl amide intermediate using the procedures set forth in R. F. C. Brown et al., *Tetrahedron Letters* **1971**, 8, 667-670<sup>9</sup> and references cited therein.

Additionally, the synthesis of a representative polycyclic  $\epsilon$ -caprolactam, i.e., a 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, is illustrated in Scheme 1. As will be readily apparent to those of ordinary skill in the art, the synthetic procedure illustrated in Scheme 1 and the reaction conditions described below can be modified by selecting the appropriate starting materials and reagents to allow the preparation of other polycyclic  $\epsilon$ -caprolactams.

Scheme 1



As shown in Scheme 1, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivatives, **6**, wherein R<sup>5</sup>, R<sup>6</sup>, *p* and *q* are as defined above, can be readily prepared in several steps from a 2-bromotoluene derivative **1** and a 2-bromoaniline derivative **4**. In this synthetic procedure, the 2-bromotoluene derivative, **1**, is first converted into the corresponding 2-methylphenylboronate ester, **2**. This reaction is typically conducted by treating **1** with about 1.0 to about 2.1 equivalents of an alkyl lithium reagent, preferably *sec*-butyl lithium or *tert*-butyl lithium, in an inert diluent, such as THF, at a temperature ranging from about -80°C to about -60°C for about 0.25 to about 1 hour. The resulting lithium anion is then treated *in situ* with an excess, preferably 1.5 equivalents, of a trialkylborate, such as trimethylborate. This reaction is initially conducted at -80°C to about -60°C and then allowed to warm to about 0°C to about 30°C for about 0.5 to about 3 hours. The resulting methyl boronate ester is typically not isolated, but is preferably converted *in situ* into the pinacol ester by treating the reaction mixture with an excess, preferably about 2.0 equivalents, of pinacol. This reaction is typically conducted at ambient temperature for about 12 to about 24 hours to afford the 2-methylphenylboronate ester, **2**, in which both R<sup>a</sup> groups are preferably joined together to form -C(CH<sub>3</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-.

In a separate reaction, the amino group of a 2-bromoaniline derivative, **3**, is converted into the *N*-Boc derivative **4** by treating **3** with about 1.0 to about 1.5 equivalents of di-*tert*-butyl-dicarbonate. Typically, this reaction is conducted at a temperature ranging from 25°C to about 100°C for about 12 to 48 hours to afford the *N*-Boc-2-bromoaniline derivative **4**.

As further illustrated in Scheme 1, the 2-methylphenylboronate ester, **2**, and the *N*-Boc-2-bromoaniline derivative **4** can then be coupled to form the biphenyl derivative **5**. This reaction is typically conducted by contacting **4** with about 1.0 to about 1.2 equivalents of **2** and about 1.0 to about 1.2 equivalents of potassium carbonate in the presence of a palladium catalyst, preferably

tetrakis(triphenylphosphine)palladium(0). Generally, this coupling reaction is conducted in a diluent, preferably 20% water/dioxane, under an inert atmosphere at a temperature ranging from about 50°C to about 100°C for about 6 to 24 hours.

5

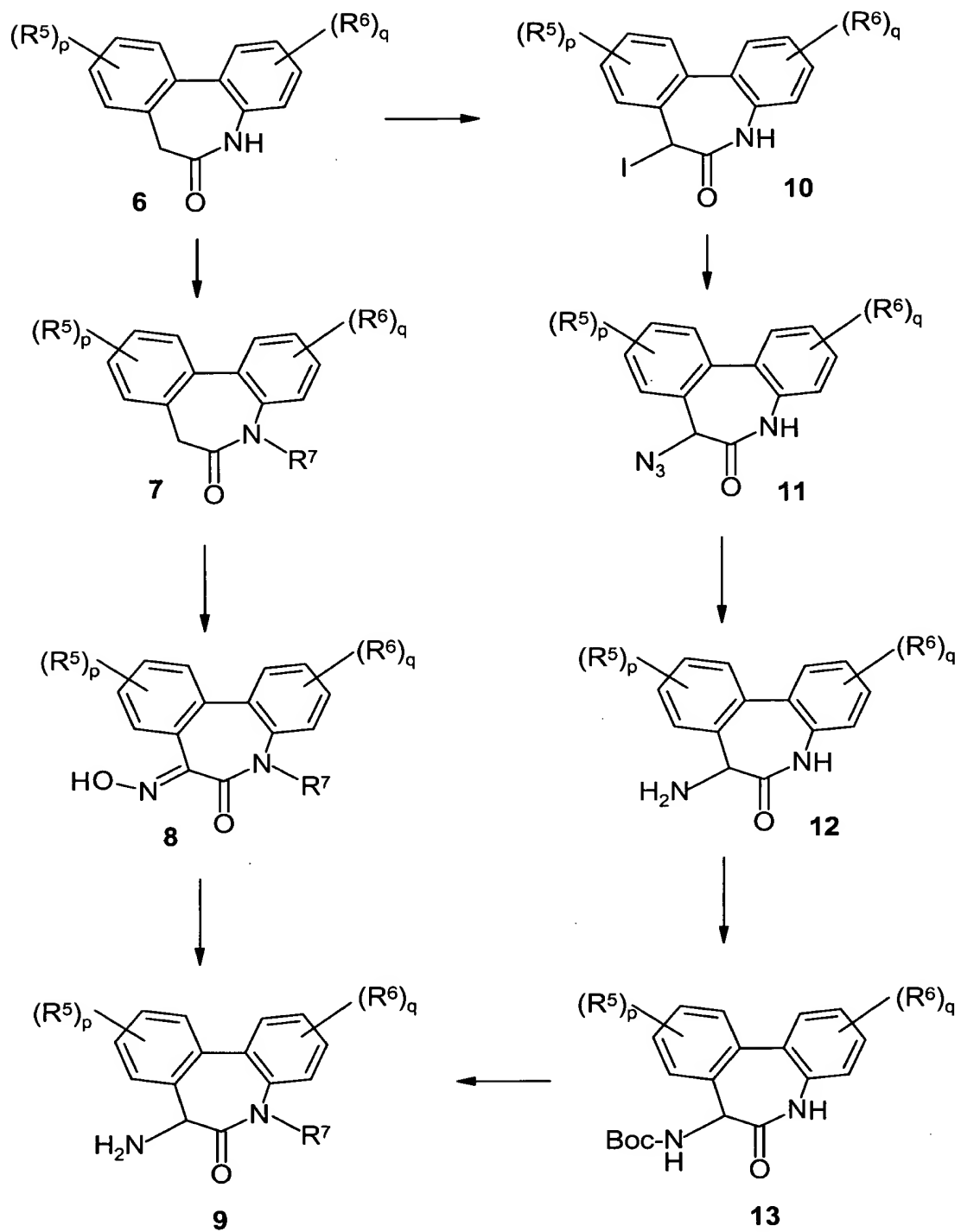
Biphenyl derivative 5 is then readily converted into the 5,7-dihydro-6H-dibenz[b,d]azepin-6-one 6 by carboxylation of the 2-methyl group, followed by cyclization to form the  $\epsilon$ -caprolactam. The carboxylation reaction is typically conducted by contacting 5 with about 2.0 to about 2.5 equivalents of a suitable base, such as *sec*-butyllithium, *tert*-butyllithium and the like, in an inert diluent, such as THF, at a temperature ranging from about -100°C to about -20°C for about 0.5 to 6 hours. The resulting dianion is then treated with excess anhydrous carbon dioxide to form the carboxylate. Treatment of the carboxylate with excess hydrogen chloride in a suitable diluent, such as methanol, at a temperature ranging from about 25°C to about 100°C then affords the 5,7-dihydro-6H-dibenz[b,d]azepin-6-one 6. Various other polycyclic  $\epsilon$ -caprolactam compounds can be prepared by routine modifications of the above described procedures.

Preferred synthetic procedures for aminating a representative polycyclic  $\epsilon$ -caprolactam compound are illustrated in Scheme 2. It will be readily apparent to those of ordinary skill in the art that the synthetic procedure illustrated in Scheme 2 and the following reaction conditions can be modified by selecting the appropriate starting materials and reagents to allow the preparation of other polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactams of this invention.

25

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Scheme 2





As shown in Scheme 2, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **6**, is optionally *N*-alkylated using conventional reagents and conditions to provide a 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative, **7**. Typically, this reaction is conducted by first contacting **6** with about 1.0 to 1.5 equivalents of a suitable base, such as sodium hydride, sodium bis(trimethylsilyl)amide and the like, in an inert diluent, such as DMF, THF and the like, at a temperature ranging from about -78°C to about 50°C for about 0.25 to about 6 hours. The resulting anion is then treated *in situ* with an excess, preferably about 1.1 to about 2.0 equivalents, of an alkyl, substituted alkyl, cycloalkyl halide, etc., typically a chloride, bromide or iodide. This reaction is typically conducted at a temperature ranging from about 0°C to about 60°C for about 1.0 to about 48 hours to afford the 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative, **7**.

The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one **7** is then oximated by contacting **7** with an excess, preferably with about 1.0 to 1.5 equivalents of a suitable base, such as sodium bis(trimethylsilyl)amide and the like, in the presence of about 1.0 to about 2.0 equivalents of an alkyl nitrite. Suitable alkyl nitrites for use in this reaction include, by way of example, butyl nitrite, isoamyl nitrite and the like. This reaction is typically conducted in an inert diluent, such as THF and the like, at a temperature ranging from about -10°C to about 20°C for about 0.5 to about 6 hours to afford the 7-alkyl-5-oximo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative **8**.

Reduction of **8** using conventional reagents and conditions then affords the 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one **9**. Preferably, this reduction reaction is conducted by hydrogenating the oxime **8** in the presence of a catalyst, such as Raney nickel. This reaction is typically conducted under about 200 psi to about 600 psi of hydrogen at a temperature of about 70°C to about 120°C for about 8 to 48 hours in a diluent, preferably a mixture of ethanol and ammonia (about 20:1). Alternatively, in another preferred procedure, the oxime

may be reduced using 10% Pd/C and between about 30 to about 60 psi of hydrogen at a temperature ranging from about 20°C to about 50°C for about 4 hours. The resulting 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one **9** is generally purified using well known procedures, such as recrystallization and/or chromatography.

Alternatively, 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, **9**, can be prepared by first forming the 5-iodo derivative **10** of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **6**. This reaction is typically conducted as described in A. O. King et al.<sup>10</sup> by treating **6** with an excess, preferably about 1.2 to about 2.5 equivalents, of trimethylsilyl iodide in the presence of an excess of a trialkylamine, such as triethylamine, diisopropylethylamine, TMEDA and the like, at a temperature ranging from about -20°C to about 0°C for about 3 to 30 minutes and then adding about 1.1 to about 2.0 equivalents of iodine (I<sub>2</sub>). Typically, after addition of the iodide, the reaction is stirred at a temperature ranging from about 0°C to about 20°C for about 2 to about 4 hours to afford 5-iodo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **10**.

Displacement of iodide from **10** using an alkali metal azide then affords 5-azido-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **11**. Typically, this reaction is conducted by contacting **10** with about 1.1 to about 1.5 equivalents of sodium azide in an inert diluent, such as DMF, at a temperature ranging from about 0°C to about 50°C for about 12 to about 48 hours.

The azido derivative **11** is then reduced to the corresponding amino derivative **12** using conventional procedures and reagents. For example, the azido group is preferably reduced by contacting **11** with an excess, preferably with about 3 equivalents, of triphenylphosphine in a diluent, preferably a mixture of THF and water. This reduction reaction is typically conducted at a

temperature ranging from about 0°C to about 50°C for about 12 to 48 hours to afford 5-amino-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **12**.

5 The amino group of **12** is then protected or blocked using a conventional amino blocking group. Preferably, compound **12** is treated with about 1.0 to about 1.1 equivalents of di-*tert*-butyl dicarbonate in the presence of an excess, preferably about 2 to about 3 equivalents, of a trialkylamine, such as triethylamine. This reaction is typically conducted in an inert diluent, such as THF, at a temperature ranging from about 0°C to about 50°C for 3 to about 24  
10 hours to provide 5-(*N*-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **13**.

Compound **13** is then optionally *N*-alkylated to afford, after de-blocking of the amino group, a 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **9**.

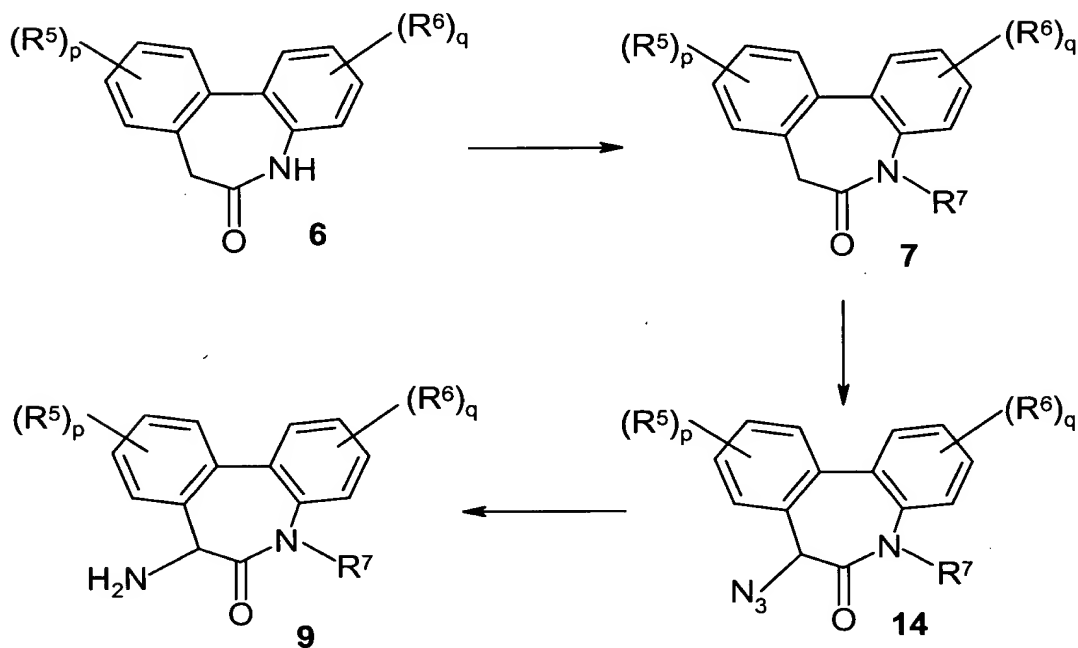
15 Representative alkyl, substituted alkyl and cycloalkyl halides suitable for use in this *N*-alkylation reaction include, by way of illustration, 1-iodo-2-methylpropane, methyl bromoacetate, 1-chloro-3,3-dimethyl-2-butanone, 1-chloro-4-phenylbutane, bromomethylcyclopropane, 1-bromo-2,2,2-trifluoroethane, bromocyclohexane, 1-bromohexane and the like.  
20

The *N*-Boc protecting group is then removed using conventional procedures and reagents to afford the 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **9**. This deblocking reaction is typically conducted by  
25 treating the *N*-Boc compound **13** with anhydrous hydrogen chloride in an inert diluent, such as 1,4-dioxane, at a temperature ranging from about 0°C to about 50°C for about 2 to about 8 hours. The resulting 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one **9** is generally purified using well known procedures, such as recrystallization and/or chromatography.

30

The 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, **9**, can also be prepared via an azide transfer reaction as illustrated in Scheme 3.

Scheme 3



As shown in Scheme 3, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, **6**, is first *N*-alkylated as described above using conventional reagents and conditions to provide a 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative, **7**.

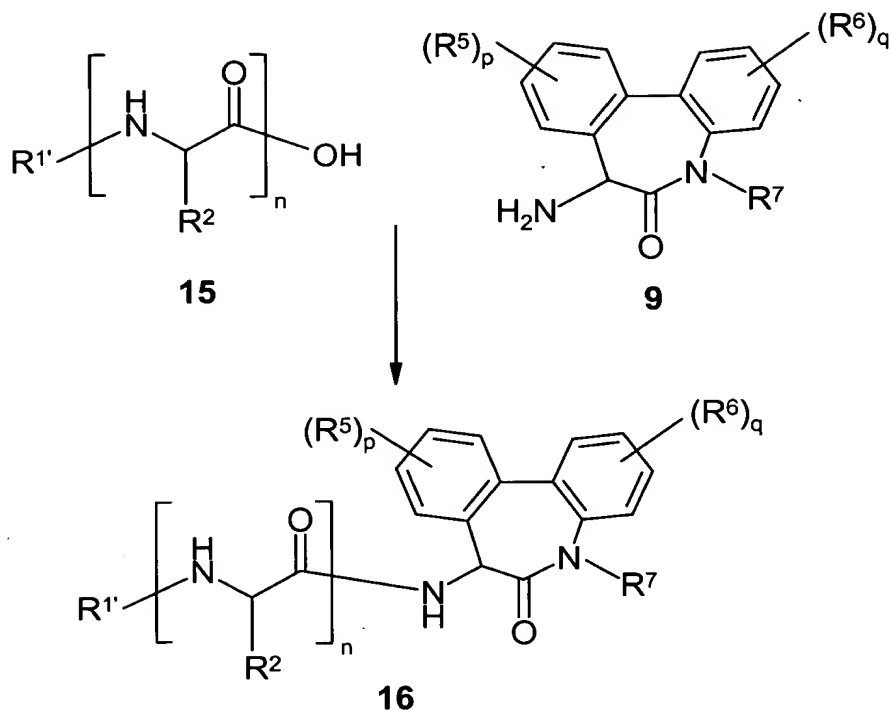
The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one **7** is then reacted with an azide transfer reagent to afford 5-azido-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one **14**. Typically, this reaction is conducted by first contacting **7** with an excess, preferably with about 1.0 to 1.5 equivalents of a suitable base, such as lithium diisopropylamine and the like, in an inert diluent such as THF, at a temperature ranging from about  $-90^{\circ}\text{C}$  to about  $-60^{\circ}\text{C}$  for about 0.25 to about 2.0 hours. The resulting anion is then treated with an excess, preferably with about 1.1 to about 1.2 equivalents, of an azide transfer reagent,

such as 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide). This reaction is typically conducted at a temperature ranging from about -90°C to about -60°C for about 0.25 to about 2.0 hours. The reaction mixture is then typically treated with an excess of glacial acetic acid and the mixture is allowed to warm to ambient temperature and then heated at about 35°C to about 50°C for about 2 to 4 hours to afford the 5-azido-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative **14**. Reduction of **14** as described above using conventional reagents and conditions then affords the 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one **9**.

If desired, the aryl rings of 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, **9**, and related compounds may be partially or fully saturated by treatment with hydrogen in the presence of a hydrogenation catalyst. Typically, this reaction is conducted by treating **9** with hydrogen at a pressure of about 10 to about 100 psi in the presence of a catalyst, such as rhodium on carbon. This reaction is typically conducted at a temperature ranging from about 20°C to about 100°C for about 12 to 96 hours in a suitable diluent, such as ethyl acetate/acetic acid (1:1) and the like.

After preparing the polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactam, the  $\alpha$ -amino group may be coupled with a mono peptide derivative (i.e., an amino acid derivative) to prepared compounds of formula I, wherein  $n$  is 1. Scheme 4 illustrates the coupling of a representative polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactam, i.e., **9**, with a mono peptide derivative **15**, wherein  $R^2$  and  $n$  are as defined above and  $R^{1'}$  is an amino-blocking group.

**Scheme 4**



As illustrated in Scheme 4, the coupling of 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, **9**, with a monoamide **15** affords the amide **16**.

This reaction is typically conducted by reacting at least a stoichiometric amount of the amino compound **9** and the monoamide **15** with a standard coupling reagent, typically in the presence of a trialkylamine, such as

5 ethyldiisopropylamine, under conventional coupling reaction conditions.

Optionally, well-known coupling promoters, such *N*-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, may be employed in this reaction. Typically, this coupling reaction is conducted at a temperature ranging from about 0°C to about 60°C for about 1 to about 72 hours in an inert diluent, such as THF, to afford the amide **16**.

Suitable coupling reagents include, by way of example, carbodiimides, such as ethyl-3-(3-dimethylamino)propylcarbodiimide (EDC), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) and the like, and other well-known coupling reagents, such as N,N'-carbonyldiimidazole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and the like. The coupling reagent may also be bound to a solid support. For example, a polymer supported form of EDC is described in *Tetrahedron Letters* **1993**, 34(48), 7685.<sup>11</sup> Additionally, 1-(3-(1-pyrrolidinyl)propyl-3-ethylcarbodiimide (PEPC) and its corresponding polymer supported forms may be used as a coupling reagent. Briefly, PEPC can be prepared by first reacting ethyl isocyanate with 1-(3-aminopropyl)pyrrolidine. The resulting urea is treated with 4-toluenesulfonyl chloride to provide PEPC. The polymer supported form is prepared by reacting PEPC with an appropriate resin, such as chloromethylated styrene/divinylbenzene resins (Merrifield's resins) under standard conditions to give the desired reagent. Such methods are described more fully in U.S. Provisional Application Serial No. 60/019,790, filed June 14, 1996,<sup>12</sup> which application is incorporated herein by reference in its entirety.

The mono peptide derivatives employed in the coupling reaction are commercially available or can be prepared using conventional procedures and reagents from commercially available starting materials. The mono peptide derivatives may be derived from naturally-occurring and non-natural amino acids. For example, suitable mono peptide derivatives (i.e., amino acid derivatives) include, by way of illustration, *N*-Boc-glycine, *N*-Boc-L-alanine, *N*-Boc-L-valine, *N*-Boc-L-leucine, *N*-Boc-L-isoleucine, *N*-Boc-*tert*-L-leucine, *N*-Boc-L-methionine, *N*-Boc-L-phenylalanine, *N*-Boc-L-phenylglycine, *N*-Boc-L-aspartic acid  $\beta$ -*tert*-butyl ester, *N*-Boc-L-glutamic acid  $\beta$ -*tert*-butyl ester, *N*-Boc-N $\epsilon$ -Cbz-L-lysine, *N*-Boc-norleucine and the like.

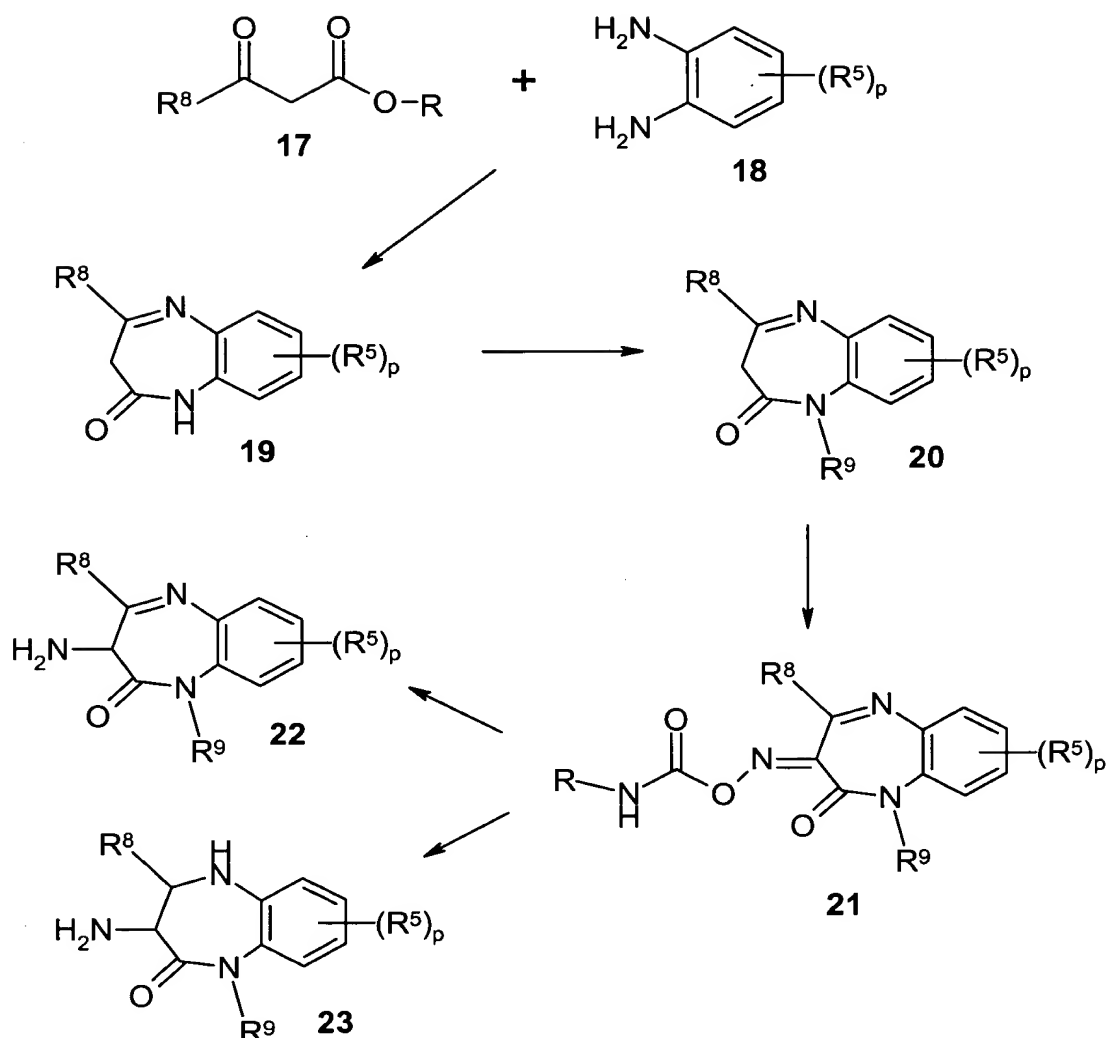
After forming amide **16**, the amino-blocking group R<sup>1'</sup>, is typically removed to reestablish the amino group. For example, when R<sup>1'</sup> is a *tert*-butoxycarbonyl group, the *N*-Boc group can be removed by treating **16** with anhydrous hydrogen chloride in an inert diluent, such as 1,4-dioxane. This reaction is typically conducted at a temperature ranging from about -10°C to about 15°C while hydrogen chloride gas is introduced into the reaction mixture, and then at a temperature ranging from about 10°C to about 60°C for about 1 to about 24 hours. Other amino-blocking groups can be removed using well-known art recognized procedures.

The substituted 1,5-diazepine compounds of this invention can be prepared as shown, for example, in Scheme 5. As illustrated in Scheme 5, a β-keto ester, **17**, where R<sup>8</sup> is as defined herein and R is typically alkyl, such as methyl, ethyl and the like, is condensed with a 1,2-phenylenediamine, **18**, where R<sup>5</sup> and *p* are as defined herein, to afford 1,3-dihydro-1,5-benzodiazepin-2-one **19**. This reaction is typically conducted by contacting **18** with an excess of **17** in an inert solvent, such as toluene, at a temperature ranging from about 50°C to about 100°C for about 2 to about 24 hours. Preferably, the water generated during the reaction is removed, for example, by using a Dean-Stark trap.

The 1,3-dihydro-1,5-benzodiazepin-2-one, **19**, is then readily alkylated using conventional reagents and reaction conditions. The *N*-alkylation reaction is typically conducted by treating **19** with about 1.0 to 1.5 equivalents of an alkyl halide, a substituted alkyl halide or a cycloalkyl halide in the presence of about 1.0 to about 1.5 equivalents of a suitable base, such as cesium carbonate and the like. This reaction is generally conducted in an inert diluent, such as DMF and the like, at a temperature ranging from about 25°C to about 100°C for about 12 to about 48 hours to afford **20**.



**Scheme 5**



The intermediate **20** is then oximated by contacting **20** with an excess, preferably with about 1.0 to 1.5 equivalents of a suitable base, such as potassium *tert*-butoxide and the like, in the presence of about 1.0 to about 2.0 equivalents of an alkyl nitrite. Suitable alkyl nitrites for use in this reaction include, by way of example, butyl nitrite, isoamyl nitrite and the like. This reaction is typically conducted in an inert diluent, such as toluene and the like, at a temperature ranging from about -20°C to about 20°C for about 0.5 to about 6 hours to afford

the corresponding 3-oximo derivative. The oxime group is then reacted with an isocyanate to afford intermediate **21**. This reaction is typically conducted by contacting the oxime derivative with about 1.0 to about 2.0 equivalents of an alkyl isocyanate, such as ethyl isocyanate, in the presence of an amine, such as triethylamine. This reaction is typically conducted in an inert diluent, such as dichloromethane and the like, at ambient temperature for about 6 to about 24 hours to afford intermediate **21**.

Reduction of intermediate **21** using, for example, zinc dust in glacial acetic acid then provides 3-amino-1,3-dihydro-1,5-benzodiazepin-2-one **22**. This reaction is typically conducted at ambient temperature for about 0.5 to about 6 hours. Alternatively, intermediate **21** can be reduced with hydrogen using a catalyst, such as palladium on carbon, to afford 3-amino-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one **23**. Typically, this reaction is conducted at ambient temperature for about 12 to about 48 hours. If desired, compounds **22** and **23** can then be coupled with an amino acid derivative using the procedures described herein.

Other methods for preparing the substituted 1,5-diazepines of this inventions are described in the Examples below.

As will be apparent to those skilled in the art, the polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactams and related compounds of this invention may contain one or more chiral centers. Typically, such compounds will be prepared as a racemic mixture. If desired, however, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) of the polycyclic  $\alpha$ -amino- $\epsilon$ -caprolactams of formula I are included within the scope of this invention. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective

reagents well known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

5     Utility

          The compounds of the invention are useful as synthetic intermediates in the preparation of inhibitors of  $\beta$ -amyloid peptide release and/or its synthesis. Accordingly, the intermediates of this inventions have utility in the preparation of compounds which are useful, for example, for diagnosing and treating  
10    Alzheimer's disease in mammals, including humans.

          For example, the use of various compounds of this invention in the preparation of inhibitors of  $\beta$ -amyloid peptide release and/or its synthesis is described in U.S. Patent Application No. 08/996,422, filed December 19,  
15    1997,<sup>13</sup> the disclosure of which is incorporated herein by reference in its entirety.

          The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

20

**EXAMPLES**

          In the examples below, the following abbreviations have the following meanings, unless otherwise indicated. All other abbreviations have their generally accepted meaning.

25

	BEMP	=	2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
	Boc	=	<i>tert</i> -butoxycarbonyl
	BOP	=	benzotriazol-1-yloxy-tris-
30			(dimethylamino)phosphonium hexafluorophosphate
	bd	=	broad doublet (spectral)
	bs	=	broad singlet (spectral)
	°C	=	degrees Celsius

	calcd	=	calculated
	$\delta$	=	chemical shift in parts per million downfield from tetramethylsilane
	d	=	doublet (spectral)
5	dd	=	doublet of doublets (spectral)
	DIC	=	diisopropylcarbodiimide
	DIPEA	=	diisopropylethylamine
	DMF	=	dimethylformamide
	DMAP	=	dimethylaminopyridine
10	DMSO	=	dimethyl sulfoxide
	EDC	=	ethyl-1-(3-dimethylaminopropyl)carbodiimide
	ee	=	enantiomeric excess
	eq.	=	equivalents
	Et	=	ethyl
15	EtOAc	=	ethyl acetate
	g	=	gram(s)
	h	=	hour(s)
	HMDS	=	1,1,1,3,3,3-hexamethyldisilazane or bis(trimethylsilyl)amine
20	HOAc	=	acetic acid
	HOBt	=	1-hydroxybenzotriazole hydrate
	HPLC	=	high-performance liquid chromatography
	Hunig's base	=	diisopropylethylamine
	IPA	=	isopropyl alcohol
25	L	=	liter
	m	=	multiplet (spectral)
	M	=	moles per liter
	max	=	maximum
	Me	=	methyl
30	meq	=	milliequivalent
	mg	=	milligram
	mL	=	milliliter
	mm	=	millimeter
	mmol	=	millimole
35	MW	=	molecular weight
	N	=	normal
	ng	=	nanogram
	nm	=	nanometers
	NMR	=	nuclear magnetic resonance
40	OD	=	optical density
	PEPC	=	1-(3-(1-pyrrolidiny)propyl)-3-ethylcarbodiimide
	PP-HOBT	=	piperidine-piperidine-1-hydroxybenzotriazole
	psi	=	pounds per square inch
	$\phi$	=	phenyl
45	q	=	quartet (spectral)

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	quint.	=	quintet (spectral)
	rpm	=	rotations per minute
	s	=	singlet (spectral)
	t	=	triplet (spectral)
5	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	tlc or TLC	=	thin layer chromatography
	$\mu$ L	=	microliter
	UV	=	ultraviolet

10

Additionally, the following abbreviations are used to indicate the commercial source for certain compounds and reagents:

15	Aldrich	=	Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233 USA
	Fluka	=	Fluka Chemical Corp., 980 South 2nd Street, Ronkonkoma NY 11779 USA
20	Lancaster	=	Lancaster Synthesis, Inc., P.O. Box 100 Windham, NH 03087 USA
	Sigma	=	Sigma, P.O. Box 14508, St. Louis MO 63178 USA
25	Bachem	=	Bachem Biosciences Inc., 3700 Horizon Drive, Renaissance at Gulph Mills, King of Prussia, PA 19406 USA
30	Novabiochem	=	Calbiochem-Novabiochem Corp. 10933 North Torrey Pines Road, P.O. Box 12087, La Jolla CA 92039-2087

35 In the examples below, all temperatures are in degrees Celsius (unless otherwise indicated). The following General Procedures were used as indicated to prepare the compounds set forth in the examples below.

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## GENERAL PROCEDURE A

### Preparation of 5-Amino-7-alkyl-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one Derivatives

5        Step A: To a stirred solution of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one  
(30 mmol) in DMF (150 mL) was added in portions 97% NaH (1.08g, 45 mmol).  
Bubbling occurred immediately and was followed by heavy precipitation. After  
10 min., an alkyl halide (33 mmol) was added. The precipitate dissolved quickly  
and in about 10 min. a clear solution was obtained. The reaction mixture was  
10 stirred overnight and then evaporated as completely as possible on a rotovap at  
30°C. Ethyl acetate (100 mL) was added to the residue and this mixture was  
washed with water, brine, and dried over magnesium sulfate. After filtration and  
concentration, the residue was typically chromatographed to provide the 7-alkyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one.

15        Step B: The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq.) from  
Step A was dissolved in THF and isoamylnitrite (1.2 eq.) was added. The  
mixture was cooled to 0°C in an ice bath. NaHMDS (1.1 eq., 1M in THF) was  
added dropwise. After stirring for 1 hour or until the reaction was complete, the  
20 mixture was concentrated then acidified with 1N HCl and extracted with EtOAc.  
The organic portion was dried and concentrated to yield a crude product which  
was purified by silica gel chromatography.

25        Step C: The resulting oxime from Step B was dissolved in EtOH/NH<sub>3</sub>  
(20:1) and hydrogenated in a bomb using Raney nickel and hydrogen (500 psi) at  
100°C for 10 hours. The resulting mixture was filtered and concentrated to  
provide a crude product which was purified by silica gel chromatography to yield  
the title compound.

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## GENERAL PROCEDURE B

### Preparation of Fluoro-Substituted 5,7-Dihydro-6H- dibenz[b,d]azepin-6-one Derivatives

5           A modification of the procedure of Robin D. Clark and Jahangir,  
*Tetrahedron* **1993**, 49(7), 1351-1356<sup>14</sup> was used. Specifically, an appropriately  
substituted *N*-Boc-2-amino-2'-methylbiphenyl was dissolved in THF and cooled  
to -78°C. *sec*-Butyllithium (1.3M in cyclohexane, 2.2 eq.) was added slowly so  
10       that the temperature remained below -65°C. The resulting mixture was allowed  
to warm to -25°C and was stirred at that temperature for 1 hour. The mixture  
was cooled to -78°C. Dry CO<sub>2</sub> was bubbled through the mixture for 30 seconds.  
The mixture was allowed to warm to ambient temperature then was carefully  
quenched with water. The mixture was concentrated under reduced pressure then  
was adjusted to pH 3 with 1N HCl. The mixture was extracted with EtOAc and  
15       the organic portion was dried and concentrated to yield a crude material. The  
crude material was dissolved in methanol and the solution was saturated with  
HCl. The mixture was heated at reflux for 12 hours then was allowed to cool.  
The mixture was concentrated to provide crude lactam which was purified by  
chromatography or crystallization.

20

## GENERAL PROCEDURE C

### Resolution of 5-Amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25       In a round bottom flask was added the racemic freebase amine (1.0 eq.) in  
methanol followed by di-*p*-toluoyl-D-tartaric acid monohydrate (1.0 eq.). The  
mixture was concentrated *in vacuo* to a residue and redissolved in a moderate  
volume of methanol and allowed to stir at room temperature open to the  
atmosphere (8-72 hours). The solid was removed by filtration. The  
enantiomeric excess was determined by chiral HPLC (Chiracel ODR) using 15%  
30       acetonitrile and 85% H<sub>2</sub>O with 0.1% trifluoroacetic acid and a flow rate of 1.0  
mL/min at 35°C. The resolved di-*p*-toluoyl-D-tartaric salt was then dissolved in

EtOAc and saturated  $\text{NaHCO}_3$  until pH 9-10 was reached. The layers were separated and the organic layer was washed again with saturated  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , and brine. The organic layer was dried over  $\text{MgSO}_4$  and the drying agent was removed by filtration. The filtrate was concentrated *in vacuo*. The free amine was dissolved in MeOH and HCl (12M, 1.0 eq.) was added. The salt was concentrated *in vacuo* and the resulting film was triturated with EtOAc. The HCl salt was filtered and rinsed with EtOAc. The ee was determined by chiral HPLC. This General Procedure can also be used to resolve other 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones.

#### GENERAL PROCEDURE D

##### EDC Coupling Procedure

A round bottom flask was charged with a carboxylic acid (1.0 eq.), hydroxybenzotriazole hydrate (1.1 eq.) and an amine (1.0 eq.) in THF under nitrogen atmosphere. An appropriate amount (1.1 eq for free amines and 2.2 eq. for hydrochloride amine salts) of base, such as Hunig's base was added to the well stirred mixture followed by EDC (1.1 eq.). After stirring from 4 to 17 hours at room temperature the solvent was removed at reduced pressure, the residue taken up in ethyl acetate (or similar solvent) and water, washed with saturated aqueous sodium bicarbonate solution, 1N HCl, brine, dried over anhydrous sodium sulfate and the solvent removed at reduced pressure to provide the product.

#### GENERAL PROCEDURE E

##### N-Boc Removal Procedure

A stream of anhydrous HCl gas was passed through a stirred solution of the N-Boc compound in 1,4-dioxane (0.03-0.09 M), chilled in a ice bath to  $\sim 10^\circ\text{C}$  under  $\text{N}_2$ , for 10-15 minutes. The cooling bath removed and the solution was allowed to warm to room temperature with stirring for 2-24 hours, monitoring by TLC for the consumption of starting material. The solution was



concentrated (and in some instances dissolved in  $\text{CH}_2\text{Cl}_2$  then re-concentrated and placed in vacuum oven at 60-70°C to remove most of the residual dioxane). The residue was typically used without further purification.

5

## GENERAL PROCEDURE F

### Reduction of Pyridines and Subsequent Acylation

#### Step A - Reduction of Pyridines

A substituted pyridine hydrochloride was dissolved in ethanol. Rhodium on alumina was added and the mixture was shaken under 60 psi atmosphere of hydrogen at 40°C for 6 to 18 hours. The mixture was filtered and concentrated to provide a crude product used in Step B.

10

#### Step B - Acylation of Piperidines

The crude product from Step A was vigorously stirred in a mixture of chloroform and saturated aqueous sodium bicarbonate. Chloroacetyl chloride (about 1.1 equivalents) was added dropwise. The resulting mixture was stirred for one hour. The organic portion was separated, dried and concentrated to provide a crude product which was purified by silica gel chromatography.

15

20

## GENERAL PROCEDURE G

### Fridel-Crafts Alkylation

An appropriately substituted chloroacetamide (1 equivalent) and aluminum trichloride (2.4 equivalents) were stirred in *o*-dichlorobenzene. The mixture was heated to between 150°C and the refluxing temperature for between one and four hours. The mixture was allowed to cool and then was poured onto ice. The mixture was extracted with methylene chloride and the organic portion was dried and concentrated to yield a crude product which was purified either by crystallization or by chromatography.

25

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## GENERAL PROCEDURE H

### Azide Transfer

The lactam starting material was dissolved in THF and the stirred solution was cooled to -78°C. An appropriate base, such as lithium diisopropylamine (1.1 eq.), was slowly added. The mixture was stirred for 30 minutes. A solution of trisyl azide (1.1 eq.) in THF was added dropwise. The resulting mixture was stirred at -78°C for 30 minutes. Glacial acetic acid (4.2 eq.) was added and the mixture was allowed to warm to room temperature. The mixture was heated to 40°C and stirred at that temperature for between 2 and 4 hours. Water was added and the mixture was extracted with ethyl acetate. The organic portion was dried and concentrated to provide a crude product which was purified by silica gel chromatography.

## GENERAL PROCEDURE I

### Azide Reduction

The azide starting material (1 eq.) was dissolved in 4% water/THF. Triphenylphosphine (2.8 eq.) was added and the mixture was stirred at ambient temperature for 16 hours. The mixture was extracted with dilute aqueous hydrochloric acid. The aqueous portion was washed with ether and then adjusted to pH 9 - 10 with aqueous sodium hydroxide. The mixture was extracted with methylene chloride. The organic portion was dried and concentrated to provide the crude amine which was purified by silica gel chromatography.

## GENERAL PROCEDURE J

### N-Alkylation Using Cesium Carbonate

To a solution of the lactam in DMF was added cesium carbonate (1.05 eq) and an alkyl iodide (1.1 eq). The mixture was allowed to stir overnight at room temperature and then the reaction mixture was diluted with ethyl acetate and washed with water, followed by brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by HPLC (LC 2000), eluting with an ethyl acetate/hexane system.

## GENERAL PROCEDURE K

### EDC Coupling Procedure

To a solution or suspension of the amine or amine hydrochloride (1.0 eq.)  
5 in THF (0.05-0.1 M) under N<sub>2</sub> at 0°C was added the carboxylic acid (1.0-1.1 eq.),  
hydroxybenzotriazole monohydrate (1.1-1.15 eq.), Hunig's base (1.1 eq. for free  
amines and 1.1-2.3 eq. for hydrochloride amine salts), followed by 1-(3-  
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1-1.15 eq.). The  
cooling bath was removed and the mixture allowed to warm to room temperature  
10 for 10-24 hours. The solution or mixture was diluted with EtOAc, in a 3-5 volume  
multiple of the initial THF volume, and washed with 0.1-1.0 M aq. HCl (1 or 2x),  
dilute NaHCO<sub>3</sub> (1 or 2x), and brine (1x). Then, the organic phase was dried over  
either MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to provide the crude product, which  
was either further purified or utilized without further purification.

15

## GENERAL PROCEDURE L

### EEDQ Coupling Procedure

To a solution of the amine in THF (1.0 eq., 0.05-0.08 M, final molarity)  
under N<sub>2</sub> at room temperature was added the N-t-Boc protected amino acid (1.1 eq.,  
20 either as a solid or in THF via cannula), followed by EEDQ (Aldrich, 1.1 eq.). The  
pale yellow solution was stirred at room temperature for 16-16.5 hours, then  
diluted with EtOAc (in a 3-5 volume multiple of the initial THF volume), and  
washed with 1M aq. HCl (2x), dilute aq. NaHCO<sub>3</sub> (2x), and brine (1x). The  
organic phase was dried over either Na<sub>2</sub>SO<sub>4</sub> or MgSO<sub>4</sub>, filtered, and concentrated.

25

Example 1

**Synthesis of  
5-Amino-7-methyl-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one Hydrochloride**

5            Step A -        Synthesis of 7-Methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A round bottom flask was charged with sodium hydride (0.295 g, 7.46 mmol) in 9.0 mL of DMF and treated with 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.3 g, 6.22 mmol) (CAS # 20011-90-9, prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* **1971**, 8, 667-670<sup>9</sup> and references cited therein). After stirring at 60°C for 1 h, the solution was treated with methyl iodide (1.16 mL, 18.6 mmol) and stirring continued for 17 h with the exclusion of light. After cooling, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O, washed with NaHSO<sub>4</sub> solution, H<sub>2</sub>O, and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation and flash chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>) gave 0.885 g (63 %) of the title compound as a colorless solid.

Physical data were as follows:

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 7.62 (d, 2H), 7.26-7.47 (m, 6H), 3.51 (m, 2H), 3.32 (s, 3H).

20            C<sub>15</sub>H<sub>13</sub>NO (MW = 223.27); mass spectroscopy (MH<sup>+</sup>) 223.

Anal. Calcd for C<sub>15</sub>H<sub>13</sub>NO; C, 80.69 H, 5.87 N, 6.27. Found: C, 80.11 H, 5.95 N, 6.23.

25            Step B -        Synthesis of 7-Methyl-5-oximo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

The product from Step A (0.700 g, 3.14 mmol) was dissolved in 20 mL of toluene and treated with butyl nitrite (0.733 mL, 6.28 mmol). The reaction temperature was lowered to 0°C and the solution was treated with KHMDS (9.42 mL, 0.5 M) under N<sub>2</sub> atmosphere. After stirring for 1 h the reaction was quenched with a saturated solution of NaHSO<sub>4</sub>, diluted with CH<sub>2</sub>Cl<sub>2</sub> and separated. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and the title compound

purified by chromatography (SiO<sub>2</sub>, 98:2 CHCl<sub>3</sub>/MeOH) giving 0.59 g (80 %) as a colorless solid.

Physical data were as follows:

C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> (MW = 252.275); mass spectroscopy (MH<sup>+</sup>) 252.

5        Anal. Calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>; C, 71.42 H, 4.79 N, 11.10. Found: C, 71.24 H, 4.69 N, 10.87.

Step C -        Synthesis of 5-Amino-7-Methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

10        The product from Step B (0.99 g, 3.92 mmol) was hydrogenated in a Parr apparatus at 35 psi over 10% Pd/C (0.46 g) in 3A ethanol. After 32 h the reaction mixture was filtered through a plug of Celite, the filtrate evaporated to a foam and treated with a saturated solution of HCl(g) in Et<sub>2</sub>O. The resulting colorless solid was filtered, rinsed with cold Et<sub>2</sub>O and vacuum dried to give 0.66 g (61%) of the title compound.

Physical data were as follows:

<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ = 9.11 (bs, 3H), 7.78-7.41 (m, 8H), 4.83 (s, 1H), 3.25 (s, 3H).

20        C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O•HCl (MW = 274.753); mass spectroscopy (MH<sup>+</sup> free base) 238.

Anal. Calcd for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O•HCl; C, 65.57 H, 5.50 N, 10.19 Found: C, 65.27 H, 5.67 N, 10.13.

Example 2

25        **Synthesis of  
5-(S)-Amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

30        Following General Procedure C using racemic 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.0 eq.) and di-*p*-toluoyl-D-tartaric acid monohydrate (1.0 eq.) in methanol, the title compound was prepared as a solid. The product was collected by filtration. Enantiomeric excess was determined by chiral HPLC.]

Physical data were as follows:

Enantiomer 1: Retention time = 9.97 minutes.

Enantiomer 2: Retention time = 8.62 minutes.

NMR data was as follows:

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  = 9.39 (s, 2H), 7.75-7.42 (m, 8H), 4.80 (s, 1H),  
3.30 (s, 3H).

$\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}$  (MW = 274.75); mass spectroscopy ( $\text{MH}^+$ ) 239.1.

Anal Calcd for  $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_3$ ; C, 65.57; H, 5.50; N, 10.20; Found: C,  
65.51, H, 5.61; N, 10.01.

10

### Example 3

#### Synthesis of

#### 5-(*N*-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

15 Step A - Synthesis of 5-Iodo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.0 g, 4.77 mmol)  
(prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* **1971**, 8,  
667-670<sup>9</sup> and references cited therein) and  $\text{Et}_3\text{N}$  ( 2.66 mL, 19.12 mmol) were  
stirred for 5.0 minutes at  $-15^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$  and treated with TMSI (1.36 mL, 9.54  
20 mmol). After stirring for 15 minutes,  $\text{I}_2$  (1.81 g, 7.16 mmol) was added in a  
single portion and the reaction allowed to warm to  $5-10^\circ\text{C}$  over 3 h. The  
reaction was quenched with sat.  $\text{Na}_2\text{SO}_3$ , diluted with  $\text{CH}_2\text{Cl}_2$  and separated. The  
organics were washed with  $\text{Na}_2\text{SO}_3$  and  $\text{NaHSO}_3$  and dried over  $\text{MgSO}_4$ . After  
filtration, the organics were concentrated to approximately 20 mL and diluted  
25 with an additional 20 mL of hexanes. The title compound was isolated as a tan  
precipitate by filtration or could be chromatographed ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{MeOH}$ , 99:1)  
to provide a yellow solid.

Physical data were as follows:

30  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  = 8.05 (bs, 1H), 7.64-7.58 (m, 2H), 7.52-7.45 (m, 2H),  
7.38-7.32 (m, 3H), 7.11 (d, 1H), 5.79 (s, 1H).

$\text{C}_{14}\text{H}_{10}\text{INO}$  (MW = 335.139); mass spectroscopy ( $\text{MH}^+$ ) 336.

Anal. Calcd for  $C_{14}H_{10}INO$ ; C, 50.17 H, 3.01 N, 4.18. Found: C, 49.97 H, 3.01 N, 4.06. .

5                    Step B -        Synthesis of 5-Azido-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

The product from Step A was dissolved in DMF and treated with 1.2 equivalents of  $NaN_3$ . After stirring 17 h at 23°C, the mixture was diluted with EtOAc/ $H_2O$ , separated, washed with brine and dried over  $MgSO_4$ . Trituration from hot EtOAc provided the title compound as a tan powder.

10                    Physical data were as follows:

$^1H$ -nmr ( $DMSO-d_6$ ):  $\delta$  = 10.51 (s, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.48 (m, 4H), 7.30 (m, 1H), 7.24 (m, 1H) 5.27 (s, 1H).

$C_{14}H_{10}N_4O$  (MW = 250.13); mass spectroscopy (MH+) 251.

15                    Step C -        Synthesis of 5-(N-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

20                    The product from Step B was dissolved in THF/ $H_2O$  and stirred at 23°C for 17 h in the presence of 3.0 equivalents of  $Ph_3P$ . The reaction was diluted with 50 % HOAc/toluene, separated, the aqueous layer extracted with toluene and evaporated to an oily residue. The pH of the residue was adjusted to pH 7.0 by the addition of 1N NaOH and the resulting HOAc salt was collected and vacuum dried. This salt was treated with di-*tert*-butyl dicarbonate (1.05 equivalents) (Aldrich) and  $Et_3N$  (2.1 equivalents) in THF. After stirring for 5 h at 23°C, the reaction was filtered and the title compound was isolated as a colorless powder.

25                    Physical data were as follows:

$^1H$ -nmr ( $CDCl_3$ ):  $\delta$  = 7.69-7.31 (m, 8H), 7.11 (m, 1H), 6.22 (m, 1H), 5.12 (m, 1H), 1.47 (s, 9H).

$C_{19}H_{20}N_2O_3$  (MW = 324.16); mass spectroscopy (MH+) 325.

30

Example 4

**Synthesis of  
5-Amino-7-(2-methylpropyl)-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one Hydrochloride**

5            Step A -        Synthesis of 5-(N-Boc-Amino)-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.2g, 0.617 mmol) (Example 3) in DMF was treated with Cs<sub>2</sub>CO<sub>3</sub> (0.22 g, 0.678 mmol) and warmed to 60°C. To the reaction mixture was added 1-iodo-2-methylpropane (0.078 mL, 0.678 mmol) and stirring continued for 17 h. After cooling to 23°C, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with several portions of brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The title compound was purified by chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH 9:1).

Physical data were as follows:

15            C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub> (MW = 380.41); mass spectroscopy (MH<sup>+</sup>) 381.

Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>; C, 72.61 H, 7.42 N, 7.36. Found: C, 72.31 H, 7.64 N, 7.17.

20            Step B -        Synthesis of 5-Amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The product from Step A was deprotected using General Procedure E to provide the title compound as a slightly colored solid after neutralization and extraction with ethyl acetate, drying over Na<sub>2</sub>SO<sub>4</sub> and vacuum drying.

Physical data were as follows:

25            <sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 7.63-7.31 (m, 8H), 4.35 (bs, 1H), 4.27 (m, 1H), 3.30 (m, 1H), 2.02 (bs, 2H), 0.55 (d, 3H), 0.29 (d, 3H).

C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O (MW = 280.17); mass spectroscopy (MH<sup>+</sup>) 281.





Example 6

**Synthesis of  
5-Amino-7-(3,3-dimethyl-2-butanonyl)-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5            Step A-        Synthesis of 5-(N-Boc-Amino)-7-(3,3-dimethyl-butanonyl)-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one  
(0.2 g, 0.617 mmol) (Example 3) in DMF was treated with Cs<sub>2</sub>CO<sub>3</sub> (0.3 g, 0.925  
mmol) and warmed to 60°C. To this reaction mixture was added 1-chloro-3,3-  
10        dimethyl-2-butanone (0.096 mL, 0.74 mmol) (Aldrich) and stirring was  
continued for 17 h. After cooling to 23°C, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>,  
washed with several portions of brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The title  
compound was isolated as a colorless solid.

Physical data were as follows:

15            C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> (MW = 422.522); mass spectroscopy (MH<sup>+</sup>) 423.

Anal. Calcd for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> · 0.6825 mol H<sub>2</sub>O; C, 69.05 H, 7.27 N, 6.44.

Found: C, 69.03 H, 7.27 N, 6.60.

20            Step B -        Synthesis of 5-Amino-7-(3,3-dimethyl-2-butanonyl)-5,7-  
dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The product from Step A was deprotected using General Procedure E to  
provide the title compound as a colorless solid after evaporation and vacuum  
drying.

Physical data were as follows:

25            <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 9.14 (bs, 3H), 7.76-7.32 (m, 8H), 4.99 (d, 1H),  
4.98 (s, 1H), 4.69 (d, 1H), 1.15 (s, 9H).

C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> HCl (MW = 358); mass spectroscopy (MH<sup>+</sup> free base) 323.

Example 7

Synthesis of

**5-Amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., *Tetrahedron Letters*, No. 8, 667-670, (1971) and references cited therein) and 1-chloro-4-phenylbutane (Aldrich), the title compound was prepared.

Physical data were as follows:

Step B: Synthesis of 5-Hydroxyimino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.37 (m, 2H), 3.65 (m, 1H), 4.50 (m, 1H) .

C<sub>15</sub>H<sub>13</sub>NO (MW = 370.45); mass spectroscopy (MH<sup>+</sup>) 371.2.

Step C: Synthesis of 5-Amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.27 (m, 2H), 3.55 (m, 1H), 4.33 (m, 1H) .

(MW = 356.47); mass spectroscopy (MH<sup>+</sup>) 357.3.

Example 8

Synthesis of

**5-Amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* **1971**, 8, 667-670<sup>9</sup> and references cited therein) and (bromomethyl)cyclopropane (Aldrich), the title compound was prepared.

Physical data were as follows:

Step B: Synthesis of 5-Hydroxyimino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.6 (m, 1H), 4.15 (m, 1H).

(MW = 292.34); mass spectroscopy (MH<sup>+</sup>) 293.2.

Example 9

**Synthesis of  
5-Amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one**

5       Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* **1971**, 8, 667-670<sup>9</sup> and references cited therein) and 1-bromo-2,2,2-trifluoroethane (Aldrich), the title compound was prepared.

Physical data were as follows:

10       Step A:       Synthesis of 7-(2',2',2'-Trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one  
                  <sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.46 (d,1H), 3.63 (d,1H), 4.07 (m, 1H), 5.06(m,1H).  
Step B:       Synthesis of 5-Hydroxyimino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one  
15       <sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 4.13 (m, 1H), 5.27 (m,1H ).  
                  (MW = 320.27); mass spectroscopy (MH+) 321.2.

Example 10

**Synthesis of  
5-Amino-7-cyclohexyl-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one**

20       Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* **1971**, 8, 667-670<sup>9</sup> and references cited therein) and  
25       bromocyclohexane (Aldrich), the title compound was prepared.

Physical data were as follows:

Step A:       Synthesis of 7-Cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one  
30       <sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.35 (d,1H), 3.47 (d,1H), 4.03 (m, 1H).

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Example 11

**Synthesis of  
5-Amino-7-hexyl-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one Hydrochloride**

5       Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* **1971**, 8, 667-670<sup>9</sup> and references cited therein) and 1-bromohexane (Aldrich), the title compound was prepared.

10                   Example 12

**Synthesis of  
5-Amino-9-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

15       Step A -       Synthesis of 4-Fluoro-2-methylphenylboronate Pinacol Ester

2-Bromo-5-fluorotoluene (1.0 eq.) (Aldrich) was stirred in THF at -78°C. *sec*-Butyllithium (1.05 eq., 1.3 M in cyclohexane) was slowly added and the mixture was stirred for 45 minutes. Trimethylborate (1.5 eq) (Aldrich) was then added and the mixture was allowed to warm to ambient temperature. After stirring for 1 hour, pinacol (2 eq.) (Aldrich) was added. The mixture was stirred for 16 hours then was concentrated under reduced pressure. The resulting residue was slurried in CH<sub>2</sub>Cl<sub>2</sub> and filtered through Celite. The filtrate was concentrated to yield an oil which was purified by chromatography on deactivated silica gel (Et<sub>3</sub>N) to yield the title compound.

25

Step B -       Synthesis of *N*-Boc-2-bromoaniline

2-Bromoaniline (1 eq.) (Aldrich) and di-*tert*-butyl-dicarbonate (1.1 eq.) (Aldrich) were stirred at 80°C for 20 hours. The resulting mixture was allowed to cool and was directly distilled using house vacuum to provide the title compound.

30

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Step C - Synthesis of N-Boc-2-amino-4'-fluoro-2'-methylbiphenyl

N-Boc-2-bromoaniline (1 eq.) (Step B), the arylboronate ester (1.1 eq.) (Step A),  $K_2CO_3$  (1.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (0.02 eq.) were stirred in 20% water/dioxane under nitrogen. The solution was heated at reflux for 10 hours. The mixture was allowed to cool then was concentrated. The resulting residue was partitioned between water and chloroform. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography using 1:1  $CH_2Cl_2$ /hexanes.

10 Step D - Synthesis of 9-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure B and using the product from Step C, the title compound was prepared.

Physical data were as follows:

15 (MW = 227.24); mass spectroscopy (MH+) 228.0.

Step E - Synthesis of 9-Fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

9-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq.) (Step D), cesium carbonate (1.1 eq.) (Aldrich) and methyl iodide (1.1 eq.) (Aldrich) were stirred in dry DMF at ambient temperature for 16 hours. The mixture was concentrated under reduced pressure to provide a residue which was partitioned between EtOAc and water. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography to provide the title compound.

Physical data were as follows:

$^1H$ -nmr ( $CDCl_3$ ):  $\delta$  = 3.33 (s, 3H), 3.42 (d, 1H), 3.54 (d, 1H).

(MW = 241.27); mass spectroscopy (MH+) 242.0.

Step F - Synthesis of 5-Amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure A, Steps B and C, and using the product from Step E, the title compound was prepared.

5 Physical data were as follows:

Gen. Proc. A/Step B: Synthesis of 5-Hydroxyimino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.44, 3.47 (singlets, 3H) .

10 (MW = 270.26); mass spectroscopy (MH<sup>+</sup>) 271.4.

Gen. Proc. A/Step C: Synthesis of 5-Amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.08 (s,2H); 3.34 (s,3H); 4.30 (s,1H).

(MW = 256.3 ); mass spectroscopy (MH<sup>+</sup>) 257.0.

15

Example 13

Synthesis of

**5-Amino-10-fluoro-7-methyl-**

**5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

20

Following the procedure of Example 12 and using 2-bromo-4-fluorotoluene (Lancaster) in Step A, the title compound was prepared.

Physical data were as follows:

Step D: Synthesis of 10-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25

<sup>1</sup>H-nmr (CDCl<sub>3</sub>/DMSO-*d*<sub>6</sub>): δ = 3.34 (q,2h); 9.91(s,1H).

(MW = 227.24); mass spectroscopy (MH<sup>+</sup>) 228.0.

Step E: Synthesis of 10-Fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.33 (s,3H), 3.42 (d,1H), 3.57 (d, 1H).

30

(MW = 241.27); mass spectroscopy (MH<sup>+</sup>) 242.0.

Step F: Synthesis of 5-Amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Gen. Proc. A/Step B: Synthesis of 5-Hydroxyimino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

35

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.43, 3.47 (singlets, 3H).

(MW = 270.26); mass spectroscopy (MH+) 271.4.

Gen. Proc. A/Step C: Synthesis of 5-Amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.06 (s, 2H); 3.34 (s, 3H); 4.28 (s, 1H).

(MW = 256.3); mass spectroscopy (MH+) 257.0.

#### Example 14

#### Synthesis of

#### 5-Amino-13-fluoro-7-methyl-

#### 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following the procedure of Example 12 and using 2-bromo-4-fluoroaniline (Lancaster) in Step B, and *o*-tolylboronic acid (Aldrich) in Step C, the title compound was prepared.

Physical data were as follows:

Step D: Synthesis of 13-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.5 (bm, 2H).

(MW = 227.24); mass spectroscopy (MH+) 227.8.

Step E: Synthesis of 13-Fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 3.33 (s, 3H), 3.35 (d, 1H), 3.52 (d, 1H).

(MW = 241.27); mass spectroscopy (MH+) 241.8.

Step F: Synthesis of 5-Amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Gen. Proc. A/Step B: Synthesis of 5-Hydroxyimino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.39, 3.44 (singlets, 3H) .

(MW = 270.26); mass spectroscopy (M+) 270.1.

Gen. Proc. A/Step C: Synthesis of 5-Amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.06 (bs, 2H); 3.33 (s, 3H); 4.35 (s, 1H).

R<sub>f</sub> (5% methanol/chloroform) = 0.3.



Example 15

**Synthesis of  
5-Amino-7-methyl-1,2,3,4,5,7-hexahydro-  
6H-dicyclohexyl[b,d]azepin-6-one**

5            5-Amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride  
(Example 1) was dissolved in a 1:1 mixture of EtOAc/HOAc. Rhodium on  
carbon (5%) was added and the mixture was stirred at 60°C under 60 psi of  
hydrogen for 3 days. The reaction mixture was then filtered and the filtrate was  
concentrated to provide an oil which was purified by SCX-cation exchange  
10 chromatography to yield the title compound.

Physical data were as follows:

(MW = 250.38); mass spectroscopy (MH<sup>+</sup>) 251.3.

Example 16

15

**Synthesis of  
(S)- and (R)-5-(L-Alaninyl)amino-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-Alaninyl)amino-7-  
methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20

N-Boc-L-Alanine (0.429 g, 2.26 mmol) (Aldrich) was dissolved in THF  
and treated with HOBt hydrate (0.305 g, 2.26 mmol), and 5-amino-7-methyl-5,7-  
dihydro-6H-dibenz[b,d]azepin-6-one (0.45 g, 1.89 mmol) (Example 1). The  
temperature was lowered to 0°C and the reaction mixture was treated with EDC  
(0.449 g, 2.26 mmol) (Aldrich) and stirred for 17 hours under N<sub>2</sub>. The reaction  
25 mixture was then evaporated and the residue diluted with EtOAc/H<sub>2</sub>O, washed  
1.0 N HCl, sat. NaHCO<sub>3</sub>, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The resulting  
diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane  
at 1.5 mL/minute.

Isomer 1: Retention time 3.37 minutes.

30

NMR data was as follows:

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 7.62-7.33 (m, 9H), 5.26 (d, 1H), 5.08 (m, 1H),  
4.34 (m, 1H), 3.35 (s, 3H), 1.49 (s, 9H), 1.40 (d, 3H).

Optical Rotation: [α]<sub>20</sub> = -96 @ 589 nm (c = 1, MeOH).

Anal. Calcd for  $C_{23}H_{27}N_3O_4$ ; C, 67.46 H, 6.64 N, 10.26. Found: C, H, 7.02 N, 9.81.

5 NMR data was as follows:

**Optical Rotation:**  $[\alpha]_{20} = 69 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).

10 Anal. Calcd for  $C_{23}H_{27}N_3O_4$ ; C, 67.46 H, 6.64 N, 10.26. Found: C, 67.40 H, 6.62 N, 10.02.

15 In separate reaction flasks, each isomer from Step A was dissolved in dioxane and treated with excess HCl(g). After stirring for 17 hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

20 C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>•HCl (MW = 345.832); mass spectroscopy (MH+ free base)  
309.

**Isomer 2:**

25      309.

Optical Rotation:  $[\alpha]_{20} = +80$  @ 589 nm (c = 1, MeOH).

## Synthesis of

5            Step A -        Synthesis of (S)- and (R)-5-(N-Boc-L-Valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Isomer 1: Retention time 3.23 minutes.  
Optical Rotation:  $[\alpha]_{20} = -120 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).  
 $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_4$  (MW = 437.544); mass spectroscopy (MH+) 438

Isomer 2: Retention time 6.64 minutes.  
Optical Rotation:  $[\alpha]_{20} = +50 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).  
 $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_4$  (MW = 437.544); mass spectroscopy (MH+) 438

25 In separate reaction flasks, each of the isomers from Step A was dissolved in dioxane and treated with excess HCl(g). After stirring for 17 hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

Optical Rotation:  $[\alpha]_{20} = -38$  @ 589 nm (c = 1, MeOH).

Isomer 2:

$C_{20}H_{23}N_3O_2 \cdot HCl$  (MW = 373.88); mass spectroscopy (MH + free base) 338.

Optical Rotation:  $[\alpha]_{20} = +97 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).

5

#### Example 18

#### Synthesis of (S)- and (R)-5-(*L*-*tert*-LeucinyI)amino-7-methyl- 5,7-dihydro-6H-dibenz[b,d]azepin-6-one

10 Step A - Synthesis of (S)- and (R)-5-(*N*-Boc-*L*-*tert*-LeucinyI)-amino-  
7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

*N*-Boc-*L*-*tert*-Leucine (0.698 g, 3.02 mmol) (Fluka) was dissolved in THF and treated with HOBt hydrate (0.408, 3.02 mmol), DIPEA (1.05 mL, 6.05 mmol) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (0.75 g, 2.75 mmol) (Example 1). The temperature was lowered to 0°C and the reaction mixture was treated with EDC (0.601 g, 3.02 mmol) (Alrich) and stirred for 17 hours under  $N_2$ . The reaction mixture was then evaporated and the residue diluted with EtOAc/ $H_2O$ , washed 1.0 N HCl, sat.  $NaHCO_3$ , brine and dried over  $Na_2SO_4$ . The diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 mL/minute.

20

Isomer 1: Retention time 3.28 minutes.

Optical Rotation:  $[\alpha]_{20} = -128 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).

$C_{26}H_{33}N_3O_4$  (MW = 451.571); mass spectroscopy (MH +) 452

Isomer 2: Retention time 5.52 minutes.

25

Optical Rotation:  $[\alpha]_{20} = +26 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).

$C_{26}H_{33}N_3O_4$  (MW = 451.571); mass spectroscopy (MH +) 452

30

Step B - Synthesis of (S)- and (R)-5-(*L*-*tert*-LeucinyI)amino-7-  
methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one  
Hydrochloride

In separate reaction flasks, each of the isomers from Step A was dissolved in dioxane and treated with excess HCl(g). After stirring for 17 hours, the title

compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

$C_{21}H_{25}N_3O_2 \cdot HCl$  (MW = 387.91); mass spectroscopy (MH + free base)

5 352.

Optical Rotation:  $[\alpha]_{20} = -34 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).

Isomer 2:

$C_{21}H_{25}N_3O_2 \cdot HCl$  (MW = 387.91); mass spectroscopy (MH + free base)

352.

10 Optical Rotation:  $[\alpha]_{20} = +108 @ 589 \text{ nm}$  ( $c = 1$ , MeOH).

#### Example 19

##### Synthesis of

15 **5-(L-Alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Step A - Synthesis of 5-(N-Boc-L-Alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 1), the title  
20 compound was prepared.

Step B - Synthesis of 5-(L-Alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the  
25 title compound was prepared.

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Example 20

**Synthesis of  
5-(L-Valinyl)amino-7-methyl-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one Hydrochloride**

5            Step A -        Synthesis of 5-(N-Boc-L-Valinyl)amino-7-methyl-5,7-  
                                 dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and  
5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 1), the title  
compound was prepared.

10

Step B -        Synthesis of 5-(L-Valinyl)amino-7-methyl-5,7-dihydro-6H-  
                                 dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the  
title compound was prepared.

15

Example 21

**Synthesis of  
5-(L-Alaninyl)amino-9-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

20            Step A -        Synthesis of 5-(N-Boc-L-Alaninyl)amino-9-fluoro-7-methyl-  
                                 5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and  
5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example  
12), the title compound was prepared.

25

Step B -        Synthesis of 5-(L-Alaninyl)amino-9-fluoro-7-methyl-5,7-  
                                 dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the  
title compound was prepared.

30

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Example 22

**Synthesis of  
5-(L-Alaninyl)amino-10-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5           Step A -       Synthesis of 5-(N-Boc-L-Alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 13), the title compound was prepared.

10

Step B -       Synthesis of 5-(L-Alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

15

Example 23

**Synthesis of  
5-(L-Alaninyl)amino-13-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

20           Step A -       Synthesis of 5-(N-Boc-L-Alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 14), the title compound was prepared.

25

Step B -       Synthesis of 5-(L-Alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

30

Example 24

**Synthesis of  
5-(L-Alaninyl)amino-7-cyclopropylmethyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5           Step A -       Synthesis of 5-(N-Boc-L-Alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 10 8), the title compound was prepared.

Step B -       Synthesis of 5-(L-Alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the 15 title compound was prepared.

Example 25

**Synthesis of  
5-(L-Alaninyl)amino-7-phenbutyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

20           Step A -       Synthesis of 5-(N-Boc-L-Alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7), the 25 title compound was prepared.

Step B -       Synthesis of 5-(L-Alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the 30 title compound was prepared.

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## Synthesis of

5            Step A -            Synthesis of 5-(N-Boc-L-Valinyl)amino-7-  
    cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-  
    one

10 8), the title compound was prepared.

Following General Procedure E and using the product from Step A, the  
15 title compound was prepared.

## Synthesis of

20 **5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**  
Step A - Synthesis of 5-(*N*-Boc-L-Valinyl)amino-7-phenbutyl-5,7-  
dihydro-6H-dibenz[b,d]azepin-6-one

25 title compound was prepared.

Following General Procedure E and using the product from Step A, the  
30 title compound was prepared.

Example 28

**Synthesis of  
5-(L-Valinyl)amino-7-hexyl-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one Hydrochloride**

5            Step A -        Synthesis of 5-(N-Boc-L-Valinyl)amino-7-hexyl-5,7-  
   dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and  
5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 11), the title  
compound was prepared.

10

Step B -        Synthesis of 5-(L-Valinyl)amino-7-hexyl-5,7-dihydro-6H-  
   dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the  
title compound was prepared.

15

Physical data were as follows:

<sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 2.17 (bm, 1H); 3.98, 4.07 (doublets, 1H); 4.27 (m,  
1H); 5.24, 5.33 (doublets, 1H).

(MW = 407.55, free base); mass spectroscopy (MH<sup>+</sup>) 408.1.

20

Example 29

**Synthesis of  
5-(L-Valinyl)amino-9-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

25            Step A -        Synthesis of 5-(N-Boc-L-Valinyl)amino-9-fluoro-7-methyl-  
   5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and  
5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example  
12), the title compound was prepared.

30

Step B -        Synthesis of 5-(L-Valinyl)amino-9-fluoro-7-methyl-5,7-  
   dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the  
title compound was prepared.

Physical data were as follows:

<sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 2.05 - 2.27 (bm, 1H); 3.96, 4.07 (doublets, 1H);  
5.26, 5.32 (doublets, 1H).

(MW = 355.41, free base); mass spectroscopy (MH<sup>+</sup>) 356.3.

5        Anal. Calcd for C<sub>20</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>2</sub>.HCl; C, 61.30 H, 5.92 N, 10.72. Found: C,  
61.15 H, 6.22 N, 10.69.

### Example 30

#### Synthesis of

10                    **5-(L-Valinyl)amino-10-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Step A -        Synthesis of 5-(N-Boc-L-Valinyl)amino-10-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

15        Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and  
5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example  
13), the title compound was prepared.

Step B -        Synthesis of 5-(L-Valinyl)amino-10-fluoro-7-methyl-5,7-  
dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

20        Following General Procedure E and using the product from Step A, the  
title compound was prepared.

Physical data were as follows:

<sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 2.05 - 2.30 (bm, 1H); 3.97, 4.06 (doublets, 1H);  
5.23, 5.32 (doublets, 1H).

25        (MW = 355.41, free base); mass spectroscopy (MH<sup>+</sup>) 356.3.

Anal. Calcd for C<sub>20</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>2</sub>.HCl; C, 61.30 H, 5.92 N, 10.72. Found: C,  
61.04 H, 5.90 N, 11.01.

Example 31

**Synthesis of  
5-(L-Valinyl)amino-13-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5           Step A -       Synthesis of 5-(N-Boc-L-Valinyl)amino-13-fluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and  
5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example  
14), the title compound was prepared.

10

Step B -       Synthesis of 5-(L-Valinyl)amino-13-fluoro-7-methyl-5,7-  
dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the  
title compound was prepared.

15

Physical data were as follows:

<sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 2.05 - 2.28 (bm, 1H); 3.98, 4.07 (doublets, 1H);  
5.27, 5.34 (doublets, 1H).

(MW = 355.41, free base); mass spectroscopy (MH<sup>+</sup>) 356.4.

Anal. Calcd for C<sub>20</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>2</sub>·HCl; C, 61.30 H, 5.92 N, 10.72. Found: C,  
20   61.24 H, 6.07 N, 10.86.

Example 32

**Synthesis of  
5-Amino-9,13-difluoro-7-methyl-  
5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

25

Following the procedure of Example 12 and using 2-bromo-4-  
fluoroaniline (Lancaster) in Step B, the title compound was prepared.

Physical data were as follows:

30

Step D:       Synthesis of 9,13-Difluoro-5,7-dihydro-6H-  
dibenz[b,d]azepin-6-one

(MW = 245.23); mass spectroscopy (MH<sup>+</sup>) 246.0.

Step F:       Synthesis of 5-Amino-9,13-difluoro-7-methyl-5,7-dihydro-  
6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.14 (s, 2H); 3.31 (s, 3H); 4.32 (s, 1H).

(MW = 274.3 ); mass spectroscopy (MH+) 275.0.

### Example 33

#### Synthesis of 5-Amino-10,13-difluoro-7-methyl- 5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following the procedure of Example 12 and using 2-bromo-4-fluorotoluene (Lancaster) in Step A and 2-bromo-4-fluoroaniline (Lancaster) in Step B, the title compound was prepared.

Physical data were as follows:

Step D: Synthesis of 10,13-Difluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

(MW = 245.23 ); mass spectroscopy (MH+) 246.0.

Step E: Synthesis of 10,13-Difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 3.30 (s,3H), 3.35 (d,1H), 3.58 (d, 1H).

Step F: Synthesis of 5-Amino-10,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.06 (s, 2H); 3.32 (s, 3H); 4.27 (s, 1H).

(MW = 274.3); mass spectroscopy (MH+) 275.0.

### Example 34

#### Synthesis of 9-Amino-5,6-dihydro-4H-quinolo[8,1-ab][3]benzazepin-8(9H)-one Hydrochloride

Step A - Synthesis of 8-Phenylquinoline

A degassed solution of 8-bromoquinoline (1.0 g, 4.81 mmol) (Aldrich) in dioxane (50 mL)/H<sub>2</sub>O (10 mL) was treated with phenylboronic acid (0.64 g, 5.29 mmol) (Aldrich), Pd(Ph<sub>3</sub>P)<sub>4</sub> (0.050 g, 0.04 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.73 g, 5.29 mmol). After refluxing for 4 h under a N<sub>2</sub> atmosphere the reaction was allowed to cool, diluted with EtOAc and separated. After drying over Na<sub>2</sub>SO<sub>4</sub> and SiO<sub>2</sub> chromatography (95:5 Hexanes/EtOAc) the titled compound was isolated as a colorless oil.

Physical data were as follows:

$^1\text{H}$ -nmr ( $\text{CDCl}_3$ ):  $\delta$  = 8.97 (d, 1H), 8.22 (dd, 1H), 7.87–7.39 (m, 9H).

$\text{C}_{15}\text{H}_{11}\text{N}$  (MW = 205); mass spectroscopy ( $\text{MH}^+$ ) 206.

Step B - Synthesis of 8-Phenyl-1,2,3,4-tetrahydroquinoline

5 The product from Step A (0.99 g, 4.82 mmol) was hydrogenated according to the procedure described by Honel, M., et. al., J.C.S. Perkin I, (1980), 1933-1938.

Physical data were as follows:

$^1\text{H}$ -nmr ( $\text{CDCl}_3$ ):  $\delta$  = 7.46 (m, 3H), 7.38 (m, 2H), 6.98 (m, 2H), 6.70 (m, 1H), 3.27 (t, 2H), 2.86 (t, 2H), 1.96 (m, 2H).

10  $\text{C}_{15}\text{H}_{15}\text{N}$  (MW = 209); mass spectroscopy ( $\text{MH}^+$ ) 210.

Step C - Synthesis of 1-Chloromethylacetyl-8-phenyl-1,2,3,4-tetrahydroquinoline

15 The product from Step B (1.0 g, 4.78 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL)/  $\text{H}_2\text{O}$  (20 mL) and treated with  $\text{NaHCO}_3$  (0.602 g, 7.18 mmol) followed by chloroacetyl chloride (0.478 ml, 5.26 mmol). After stirring for 17 h at  $23^\circ\text{C}$ , the reaction was diluted with  $\text{CH}_2\text{Cl}_2$ , washed with saturated  $\text{NaHCO}_3$ , dried over  $\text{Na}_2\text{SO}_4$  and purified by  $\text{SiO}_2$  chromatography ( $\text{CHCl}_3$ /Hexanes 9:1). The product was isolated as a colorless solid.

20 Physical data were as follows:

$\text{C}_{17}\text{H}_{16}\text{ClNO}$  (MW = 286.77); mass spectroscopy ( $\text{MH}^+$ ) 287.

Anal. Calcd for  $\text{C}_{17}\text{H}_{16}\text{ClNO}$ ; C, 71.45 H, 5.64 N, 4.90. Found: C, 71.63 H, 5.60 N, 4.87.

25 Step D - Synthesis of 5,6-Dihydro-4H-quinol[8,1-ab][3]benzazepin-8(9H)-one

30 The product from Step C (0.89 g, 3.11 mmol) was mixed thoroughly with  $\text{AlCl}_3$  (0.87 g, 6.54 mmol) at  $23^\circ\text{C}$  and the mixture heated neat at  $100^\circ\text{C}$  for 5-7 minutes. After vigorous gas evolution, the molten mixture was allowed to cool and extracted with several portions of  $\text{CH}_2\text{Cl}_2$ / $\text{NaHCO}_3$  (sat). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the title compound was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3$ /hexanes 9:1), yielding a colorless oil which solidified upon standing.

5

15

20

## 25

30

Physical data were as follows:  
 $C_{17}H_{16}N_2O$  (MW = 264.326); mass spectroscopy (MH+ ) 266.  
 Anal. Calcd for  $C_{17}H_{16}N_2O$ ; C, 77.25 H, 6.10 N, 10.60. Found: C, 77.23 H,  
 6.15 N, 10.49.

Example 35

Synthesis of

**9-(N'-L-Alaninyl)amino-5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one Hydrochloride**

5

Step A - Synthesis of 9-(N'-Boc-L-Alaninyl)amino-5,6-Dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one

Following General Procedure D and using N-Boc-Alanine (Aldrich) and 9-amino-5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one (from Example 34), the title compound was prepared.

10

Physical data were as follows:

$C_{25}H_{29}N_3O_4$  (MW = 435.521); mass spectroscopy (MH + ) 436.

Anal. Calcd for  $C_{25}H_{29}N_3O_4 \cdot 0.4102$  mol  $H_2O$ ; C, 67.79 H, 6.79 N, 9.49;

Found: C, 67.83 H, 6.91 N, 9.29.

15

Step B - Synthesis of 9-(N'-L-Alaninyl)amino-5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

20

Physical data were as follows:

$C_{20}H_{21}N_3O_2 \cdot HCl$  (MW = 371.6); mass spectroscopy (MH + free base )

335.

Example 36

Synthesis of

**7-Amino-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one**

25

Step A - Synthesis of N-Chloroacetyl-2-benzylpiperidine

Following General Procedure F and using 2-benzylpyridine, the title compound was prepared.

30

Physical data were as follows:

(MW = 251.8); mass spectroscopy (MH + ) 252.0.



Step B - Synthesis of 1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one

Following General Procedure G and using *N*-chloroacetyl-2-benzylpiperidine, the title compound was prepared.

5 Physical data were as follows:

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 1.3-1.9 (6H); 2.42 (t, 1H); 3.08 (m, 2H); 3.47 (m, 1H); 3.96 (q, 2H); 4.66 (d, 1H); 7.2 (m, 4H).

(MW = 215.3); mass spectroscopy (MH<sup>+</sup>) 216.1.

10 Step C - Synthesis of 7-Oximo-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one

Following General Procedure A (Step B) and using 1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one (from Step B), the title compound was prepared.

15 Physical data were as follows:

(MW = 244.3); mass spectroscopy (MH<sup>+</sup>) 245.0.

Step D - Synthesis of 7-Amino-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one

20 Following General Procedure A (Step C) and using 7-oximo-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one (from Step C), the title compound was prepared.

Physical data were as follows:

25 <sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 1.3-1.9 (6H); 2.42 (t, 1H); 3.08 (m, 2H); 3.47 (m, 1H); 3.96 (q, 2H); 4.66 (d, 1H); 7.2 (m, 4H).

(MW = 230.3); mass spectroscopy (MH<sup>+</sup>) 231.1.

30

Example 37

**Synthesis of  
1-(N'-L-Alaninyl)amino-4,5,6,7-tetrahydro-  
3,7-methano-3H-3-benzazonin-2(1H)-one**

5           Step A -       Synthesis of N-Chloroacetyl-3-phenylpiperidine

Following General Procedure F and using 3-phenylpyridine hydrochloride (Aldrich), the title compound was prepared.

10           Step B -       Synthesis of 4,5,6,7-Tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure G and using N-chloroacetyl-3-phenylpiperidine, the title compound was prepared.

Physical data were as follows:

15           <sup>1</sup>H-nmr (CDCl<sub>3</sub>): d = 1.32-1.57 (2H); 2.08 (m, 2H); 2.81 (t, 1H); 3.13 (bs, 1H); 3.37 (m, 2H); 4.36 (m, 2H); 4.50 (d, 1H).

(MW = 201.3); mass spectroscopy (MH<sup>+</sup>) 202.1.

20           Step C -       Synthesis of 1-Oximo-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure A (Step B) and using the product from Step B, the title compound was prepared.

25           Step D -       Synthesis of 1-Amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure A (Step C) and using the product from Step C', the title compound was prepared.

Physical data were as follows:

<sup>1</sup>H-nmr (CDCl<sub>3</sub>): δ = 2.86 (t, 1H); 3.17 (bs, 1H); 3.39 (dd, 1H); 4.40 (d, 1H); 4.50 (d, 1H); 5.39 (s, 1H).

30           (MW = 216.3); mass spectroscopy (MH<sup>+</sup>) 217.4.

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Following General Procedure D and using *N*-tert-Boc-L-alanine (Aldrich) the product from Step D, the title compound was prepared.

Step F - Synthesis of 1-(N'-L-Alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure E and using the product from Step E, the title compound was prepared.

Example 38 Omitted

Step A - Synthesis of 1,3-Dihydro-4-phenyl-(2H)-1,5-benzodiazepin-2-one (CAS No. 16439-95-5)

The following procedure is adapted from G. Vernin et al., *Chemica Scripta* **1980**, *16*, 157-162. A mixture of 1,2-phenylenediamine (5.00 g, 46.2 mmol, Aldrich) and ethyl benzoylacetate (9.77 g, 50.8 mmol, Aldrich) in toluene (150 mL) was heated to reflux for 4 hours, while removing water with a Dean-Stark trap. Upon cooling to ambient temperature, the product crystallized and was collected by filtration. The precipitate was rinsed with toluene (100 mL) to afford the title intermediate (8.0 g, 73%) as an off-white solid, m.p. 208-209°C.

Physical data were as follows:  
C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O (MW 236.27), mass spectroscopy, MH<sup>+</sup> 237.2.

Analytical for  $C_{15}H_{12}N_2O$ : Theory, C, 76.25; H, 5.12; N, 11.86. Found, C, 76.52; H, 4.96; N, 11.75.

$^1H$ -NMR ( $CDCl_3$ , 250 MHz):  $\delta$  = 9.39 (bs, 1H), 8.08-8.11 (m, 2H), 7.51-7.45 (m, 4H), 7.27-7.18 (m, 2H), 7.13-7.09 (m, 1H), 3.56 (s, 2H).

5

Step B - Synthesis of 1,3-Dihydro-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one (CAS No. 58876-61-2)

To a solution of the product from Step A (6.00 g, 25.4 mmol) in DMF (120 mL) was added cesium carbonate (9.11 g, 27.9 mmol) and iodomethane (1.74 mL, 27.9 mmol). The mixture was stirred at ambient temperature overnight, then diluted with EtOAc (300 mL) and washed with water (200 mL). The organic layer was dried over  $Na_2SO_4$ , filtered, and concentrated. HPLC purification eluting with hexanes/EtOAc (6:4) afforded the title intermediate 5.80 g (92%) as a yellow oil.

15

Physical data were as follows:

$C_{16}H_{14}N_2O$  (MW 250.30), mass spectroscopy,  $MH^+$  251.1.

Analytical for  $C_{16}H_{14}N_2O$ : Theory, C, 76.78, H, 5.64, N, 11.19. Found, C, 76.97, H, 5.34, N, 11.11.

$^1H$ -NMR ( $CDCl_3$ , 300 MHz):  $\delta$  = 8.16-8.10 (m, 2H), 7.50-7.42 (m, 4H), 7.33-7.23 (m, 3H), 4.14 (bd, 1H,  $J$  = 10.25 Hz), 3.38 (s, 3H), 2.99 (bd, 1H,  $J$  = 11.71 Hz).

20

Step C - Synthesis of 1,3-Dihydro-3-oximido-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one

25

This step was conducted using the general procedure of G. A. Showell et al., *J. Med. Chem.* **1994**, 37, 719. To a solution of the product from Step B (1.0 g, 4.0 mmol) in toluene (32 mL) at  $-20^\circ C$  was added potassium *t*-butoxide (1.12 g, 10.0 mmol) in two portions. The resulting orange solution was stirred for 20 minutes, then isoamyl nitrite (0.64 mL, 4.8 mmol) was added and the solution stirred for an additional 5 hrs at  $-20^\circ C$ . The reaction was quenched with  $H_2O$  (8 mL) containing citric acid (840 mg). After 10 minutes,  $Et_2O$  (8 mL) was added and the suspension stirred at ambient temperature overnight. The mixture was diluted with EtOAc (200 mL) and washed with water (100 mL). The organic layer was

30

dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes / EtOAc (1:1) afforded the title intermediate (1.10 g, 98%) as a yellow solid exhibiting an ~10:1 mixture of oxime isomers, m.p. 233-234°C.

Physical data were as follows:

5 C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> (MW 279.30), mass spectroscopy, MH<sup>+</sup> 280.2, MH<sup>-</sup> 278.2.

Analytical for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: Theory, C, 68.81; H, 4.69; N, 15.04. Found, C, 68.79; H, 4.69; N, 14.77.

<sup>1</sup>H NMR (D<sub>6</sub>-DMSO, 300 MHz): δ = 12.26 (bs, 1H), 7.91-7.88 (m, 2H), 7.58-7.48 (m, 5H), 7.40-7.30 (m, 2H), 3.38 (s, 3H).

10

Step D - Synthesis of 1,3-Dihydro-3-(oximido-ethyl-carbamoyl)-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one

To a solution of the product from Step C (1.14 g, 4.08 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added Et<sub>3</sub>N (568 μL, 4.08 mmol) followed by ethyl isocyanate (387 μL, 4.89 mmol) and the solution stirred at ambient temperature overnight. Then the solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and washed with water (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes/EtOAc (1:1) afforded the title intermediate (1.30 g, 92%) as an ~ 4:1 mixture of oxime isomers as pale yellow solid, m.p. 178-179°C.

15

20

Physical data were as follows:

C<sub>19</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub> (MW 350.38), mass spectroscopy, MH<sup>-</sup> 351.5.

Analytical for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>: Theory, C, 65.13; H, 5.18; N, 15.99. Found, C, 65.41; H, 5.27; N, 16.03.

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 Mhz) (major isomer): δ = 7.98-7.95 (m, 2H), 7.53-7.44 (m, 4H), 7.32-7.28 (m, 3H), 5.88 (bt, 1H, J=5.09 Hz), 3.48 (s, 3H), 3.28-3.16 (m, 2H), 1.10 (t, 3H, J=7.1Hz).

Step E - Synthesis of 1,3-Dihydro-3-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one

To a stirred mixture of the product from Step D (2.5 g, 7.1 mmol) in glacial AcOH (44 mL), H<sub>2</sub>O (22 mL) and MeOH (64 mL) was added zinc dust (1.76 g, 26.9 mmol). The reaction mixture stirred for 1 hour at room temperature, monitoring by TLC. The reaction mixture was poured into aq. 1N HCl (100 mL), and further diluted with water (100 mL), then washed with EtOAc (100 mL). The aqueous layer was made basic (to pH ~9-10) with 2N aq. NaOH and the product extracted into cold EtOAc (200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give 1.28 g (55%) of the title intermediate as a light orange solid.

Physical data were as follows:

C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O (MW 265.32), mass spectroscopy, MH<sup>+</sup> 266.1.

Example 40

Synthesis of

**1,3-Dihydro-3-(L-alaninyl)-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride**

Step A - Synthesis of 1,3-Dihydro-3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one

To a solution of the product from Example 39, Step E (0.720 g, 2.7 mmol) in THF (20 mL) was added (L)-Boc-alanine (0.588 g, 2.98 mmol), HOBT (0.403 g, 2.98 mmol), EDC (0.573 g, 2.98 mmol), and N,N-diisopropylethylamine (0.52 mL, 2.98 mmol). The resulting mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with EtOAc (100 mL), then washed with H<sub>2</sub>O (100 mL), 1M aq. K<sub>2</sub>CO<sub>3</sub> (50 mL), and brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated.

HPLC purification eluting with hexanes/EtOAc (6:4) afforded 700 mg (60%) of the title intermediate as a yellow solid, m.p. 90-91 °C.

Physical data were as follows:

$C_{24}H_{28}N_4O_4$  (MW 436.51), mass spectroscopy,  $MH^+$  437.3,  $MH^-$  435.4.

5      Anal. Calcd. for  $C_{24}H_{28}N_4O_4$ : Theory, C; 66.04; H, 6.47; N, 12.84.  
Found, C, 65.91; H, 6.60; N, 12.70.

Step B -      Synthesis of 1,3-Dihydro-3-(L-alaninyl)-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride

10      Through a solution of the product from Step A (1.5 g, 3.5 mmol) in 1,4-dioxane (200 mL) was passed a stream of HCl gas for 5 minutes. The reaction flask was capped and the solution stirred overnight at ambient temperature. The solution was concentrated to give 0.5 g (39%) of the title intermediate as a white solid, m.p. 196-198 °C.

15      Physical data were as follows:

$C_{19}H_{21}N_4O_2Cl$  (MW 372.85), mass spectroscopy,  $MH^+$  (minus HCl) 337.2,  $MH^-$  (minus HCl) 335.

Exact Mass. Calcd. for  $C_{19}H_{21}N_4O_2$ : Theory 337.1664, Found .337.1650

20

Example 41

Synthesis of

**1,3,4,5-Tetrahydro-3-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one**

25

To a mixture of 10% Pd/C (200 mg) in EtOH (15 mL) was added the product from Example 39, Step D (200 mg, 0.571 mmol) and the vessel atmosphere charged with hydrogen via a balloon. The reaction mixture was stirred overnight at ambient temperature. The mixture was filtered through Celite and the filtrate concentrated to afford 144.0 mg (95 %) of the title intermediate as a pale yellow amorphous solid.

Physical data were as follows:

$C_{13}H_{17}N_3O$  (MW 267.330)

Exact Mass. Calcd. for  $C_{16}H_{18}N_3O_2$ : Theory 268.1450, Found 268.1432.

#### Example 42

##### Synthesis of

##### **1,3,4,5-Tetrahydro-3-(L-alaninyl)-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride**

Step A - Synthesis of 1,3,4,5-Tetrahydro-3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one

To a solution of the product from Example 41 (1.5 g, 5.6 mmol) in THF (100 mL) was added (L)-Boc-alanine (1.15 g, 6.2 mmol), HOBT (0.831 g, 6.2 mmol), EDC (1.18 g, 6.2 mmol), and N,N-diisopropylethylamine (1.07 ml, 6.2 mmol). The resulting mixture was stirred at ambient temperature overnight. The mixture was diluted with EtOAc (200 mL) and washed with H<sub>2</sub>O (200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes/EtOAc (6:4) afforded 1.2 g (49%) of the title intermediate as a white solid, m.p. 92-93°C.

Physical data were as follows:

$C_{24}H_{30}N_4O_4$  (MW 438.525), mass spectroscopy, MH<sup>+</sup>439.2.



Exact Mass. Calcd. for  $C_{24}H_{31}N_4O_4$ : Theory 439.2345, Found 439.2325

Step B - Synthesis of 1,3,4,5-Tetrahydro-3-(L-alaninyl)-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride

Through a solution of the product from Step A (1.2 g, 2.7 mmol) in 1,4-dioxane (200 mL) was passed a stream of HCl gas for 5 minutes. The reaction flask was capped and the solution stirred overnight at ambient temperature. The solution was concentrated to give 1.0 g (100%) of the title intermediate as a white solid, m.p 200-202°C.

Physical data were as follows:

$C_{19}H_{23}N_4O_2Cl$  (MW 374.870), mass spectroscopy,  $MH^+$  375.3,  $MH^-$  373.2.

Exact Mass. for  $C_{19}H_{23}N_4O_2$ : Theory 339.1821, Found 339.1824.

Example 43

Synthesis of

**1,3-Dihydro-3-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one**

Step A - Synthesis of 1,3-Dihydro-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

The following procedure is adapted from G. Vernin et al., *Chemica Scripta* 1980, 16, 157-162. A mixture of 1,2-phenylenediamine (1.86 g, 17.2 mmol, Aldrich) and ethyl isobutyrylacetate (3.0 g, 18.9 mmol, Aldrich) in toluene (80 mL) was heated to reflux under nitrogen for 4 hours, while removing water with a Dean-Stark trap. Upon cooling to ambient temperature, the product crystallized and was collected by filtration, rinsing with toluene (100 mL), then slurried in Et<sub>2</sub>O and filtered to give 2.16 g (62%) of the title intermediate as an off-white solid, m.p. 167-168°C.

Physical data were as follows:

C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O (MW 202.26), mass spectroscopy, MH<sup>+</sup>203.1.

Analytical for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O: Theory, C, 71.26, H, 6.97, N, 13.85. Found, C, 71.13, H, 6.67, N, 14.06.

<sup>1</sup>H-NMR (D<sub>6</sub>-DMSO, 300 MHz): δ = 10.33 (bs, 1H), 7.24-7.10 (m, 4H), 3.03 (s, 2H), 2.77 (septet, 1H, J= 6.86), 1.16 (d, 6H, J= 6.59 Hz).

Step B - Synthesis of 1,3-Dihydro-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

To a solution of the product from Step A (2.18 g, 10.8 mmol) in DMF (20 mL) was added cesium carbonate (3.87 g, 11.8 mmol), and iodomethane (0.74 mL, 11.8 mmol). The mixture was stirred at ambient temperature overnight, then diluted with EtOAc (200 mL), and washed with water (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes/EtOAc (3:7) afforded 1.90 g (88%) of the title intermediate as a yellow oil. Physical data were as follows:

C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O (MW 216.282), mass spectroscopy, MH<sup>+</sup> 217.1.

Exact Mass . for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O: Theory 217.1341; Found, 217.1327.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.30-7.15 (m, 4H), 3.49 (bd, 1H, J= 11.71 Hz), 3.36 (s, 3H), 2.81 (septet, 1H, J= 6.83 Hz), 2.74 (bd, 1H, J= 12.81 Hz), 1.24 (bd, 6H, J= 6.22 Hz).

5                    Step C -        Synthesis of 1,3-Dihydro-3-oximido-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

                  This step was conducted following the general procedure of G. A. Showell et al., *J. Med. Chem.* **1994**, 37, 719. To a solution of the product from Step C (1.0 g, 4.9 mmol) in toluene (30 mL) at -20°C was added potassium *t*-butoxide (1.38 g, 12.3 mmol) in two portions. The resultant pale yellow solution was stirred at -20°C for 20 minutes, then allowed to warm to 0°C with stirring for 5 minutes. Isoamyl nitrite (0.80 mL, 5.9 mmol) was added to the orange solution and the solution stirred at -20°C for an additional 5 hrs. The reaction quenched with H<sub>2</sub>O (8 mL) containing citric acid (840 mg) and stirred 10 minutes allowing the mixture to warm. Then, Et<sub>2</sub>O (8 mL) was added and the suspension stirred at ambient temperature overnight. The mixture was diluted with EtOAc (200 mL) and washed with water (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes / EtOAc (3:7) afforded 760 mg (63 %) of the title intermediate as an ~3:1 mixture of oxime isomers, and as a pale yellow solid, m.p. 140-144°C.

Physical data were as follows:

C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> (MW 245.28), mass spectroscopy, MH<sup>+</sup> 246.3, MH<sup>-</sup> 244.4

Exact Mass.for C<sub>13</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>: Theory 246.1243; Found 246.1237

25                    <sup>1</sup>H-NMR (D<sub>6</sub>-DMSO, 300 Mhz) (major isomer): δ = 12.25 (s, 1H), 7.51-7.44 (m, 1H), 7.33-7.21 (m, 3H), 3.35 (s, 3H), 3.14 (septet, 1H, J=6.95 Hz), 1.24 (d, 3H, J=6.59), 1.12 (d, 3H, J=7.32).

Step D -        Synthesis of 1,3-Dihydro-3-(oximido-ethyl-carbamoyl)-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

To a solution of the product from Step C (4.0 g, 16.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 mL) was added  $\text{Et}_3\text{N}$  (2.73 mL, 19.6 mmol) followed by ethyl isocyanate (1.55 mL, 19.6 mmol) and the solution stirred at ambient temperature overnight. The solution was diluted with  $\text{CH}_2\text{Cl}_2$  (300 mL), and washed with water (150 mL) then brine (150 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The resulting solid was slurried in  $\text{Et}_2\text{O}$ /hexanes (1:1) and collected by vacuum filtration washing with  $\text{Et}_2\text{O}$ /hexanes (1:1, 100 mL) to afford 3.51 g (68%) of the title intermediate as a white solid, m.p. 177-179°C.

Physical data were as follows:

$\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_3$  (MW 316.36), mass spectroscopy,  $\text{MH}^+$  317.1.

Analytical for  $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_3$ : Theory, C, 60.75; H, 6.37; N, 17.71. Found, C; 60.67; H, 6.37; N, 17.47.

Step E - Synthesis of 1,3-Dihydro-3-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

To a stirred mixture of the product from Step D (2.0 g, 7.57 mmol) in glacial AcOH (44 mL),  $\text{H}_2\text{O}$  (22 mL), and MeOH (64 mL) was added zinc dust (1.77 g, 27.0 mmol). The reaction mixture stirred for 1 hour at room temperature, monitoring by TLC. The reaction mixture was diluted with 1N aq. HCl (100 mL) and water (100 mL), then washed with EtOAc (100 mL). Aqueous layer made basic to pH ~9-10 with 2N aq. NaOH and the product extracted into cold EtOAc (200 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give 1.06 g (61 %) of the title intermediate as a tan solid.

Physical data were as follows:

$\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}$  (MW 231.297), mass spectroscopy,  $\text{MH}^+$  232.1.

Exact Mass. Calcd. for  $\text{C}_{13}\text{H}_{18}\text{N}_3\text{O}_2$ : Theory 232.1450, Found 232.1448.

**1,3-Dihydro-3-(L-alaninyl)-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride**

## 5

10

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Exact Mass. Calcd. for  $C_{21}H_{31}N_4O_4$ : Theory 403.2345, Found 403.2343.

## 25

Through a solution of the product from Step B (1.35 g, 3.47 mmol) in 1,4-dioxane (200 mL) was passed a stream of HCl gas for 5 minutes. The reaction flask was capped and the solution stirred overnight at ambient temperature. The solution was concentrated to give 480 mg (41%) of the title intermediate as a white solid, m.p 190-196°C.

Physical data were as follows:

$C_{16}H_{23}N_4O_2Cl$  (MW 338.837), mass spectroscopy,  $MH^+$  303.2 (minus HCl).

Analytical for : $C_{16}H_{23}N_4O_2Cl \cdot 5H_2O$  Theory, C;55.24; H, 6.95; N, 16.10.

Found, C; 55.12; H, 6.60; N, 15.59.

Exact Mass. for : $C_{16}H_{23}N_4O_2$ : Theory 303.1821, Found 303.1803.

5

#### Example 45

##### Synthesis of

##### **1,3,4,5-tetrahydro-3-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one**

10

To a suspension of 10% Pd/C (900 mg) in EtOH (160 mL) was added the product from Example 43, Step D (1.6 g, 6.9 mmol) and the flask charged with a hydrogen atmosphere via a balloon. The reaction mixture was stirred overnight at ambient temperature. Then filtered through Celite and the filtrate concentrated to give 1.19 g (70 %) of the title intermediate as a pale yellow oil.

15

Physical data were as follows:

$C_{13}H_{19}N_3O$  (MW 233.313).

Exact Mass. Calcd. for  $C_{13}H_{20}N_3O_2$ : Theory 234.1606, Found 234.1583.

20

#### Example 46

##### Synthesis of

##### **1,3,4,5-Tetrahydro-3-(L-alaninyl)-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride**

25

Step A - Synthesis of 1,3,4,5-Tetrahydro-3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

30

To a solution of the product from Example 45 (1.09 g, 4.6 mmol) in THF (75 mL) was added (L)-Boc-alanine (960 mg, 5.1 mmol), HOBT (693 mg, 5.1

mmol), EDC (985 mg, 5.1 mmol), and N,N-diisopropylethylamine (897  $\mu$ l, 5.1 mmol). The resulting mixture was stirred ambient temperature overnight. The mixture was diluted with EtOAc (200 mL), then washed with H<sub>2</sub>O (200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes/EtOAc (6:4) afforded 1.5 g (80%) of the title intermediate as a white solid, m.p. 194-195°C.

Physical data were as follows:

C<sub>21</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub> (MW 403.508), mass spectroscopy, MH<sup>+</sup> 405.5.

Analytical for C<sub>21</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>: Theory, C; 62.35, H; 7.97, N, 13.85.

Found, C; 62.62, H; 7.80, N, 14.14.

Step B - Synthesis of 1,3,4,5-Tetrahydro-3-(L-alaninyl)-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride

Through a solution of the product from Step A (1.5 g, 3.7 mmol) in 1,4-dioxane (200 mL) was passed a stream of HCl gas for 5 minutes. The reaction flask was capped and the solution stirred overnight at ambient temperature. The solution was concentrated to give 0.9 g (71%) of the title intermediate as a white solid, m.p. 202-203°C.

Physical properties were as follows:

C<sub>16</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>Cl (MW 340.853), mass spectroscopy, MH<sup>+</sup> (minus HCl) 305.2.

Exact Mass. Calcd. for C<sub>16</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>: Theory 305.1997, Found 305.1967.

Example 47

**Synthesis of  
1,3-Dihydro-3-[(L)-norleucinyl]amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride**

Step A - Synthesis of 1,3-Dihydro-3-[N'-(t-butoxycarbonyl)-L-norleucinyl]-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

To a solution of the product from Example 43, Step E (2.50 g, 10.8 mmol) in THF (200 mL) was added (L)-Boc-Nva-OH (2.58 g, 11.9 mmol, Bachem), HOBT (1.60 g, 11.9 mmol), EDC (2.28 g, 11.9 mmol), and N,N-diisopropylethylamine (2.07 mL, 11.9 mmol). The resulting mixture was stirred at ambient temperature overnight. The mixture was diluted with EtOAc (300 mL) and washed with 1N aq. HCl (100 mL), 1M aq. K<sub>2</sub>CO<sub>3</sub> (100 mL), and brine (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes/EtOAc (6:4) afforded 3.20 g (69 %) of the title intermediate as a pale yellow solid.

Physical data were as follows:

C<sub>23</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub> (MW 430.546), mass spectroscopy, MH<sup>+</sup> 430.4, MH<sup>-</sup> 429.4  
Exact Mass. Calcd. for C<sub>23</sub>H<sub>35</sub>N<sub>4</sub>O<sub>4</sub>: Theory 431.2658, Found 431.2658.

Step B - Synthesis of 1,3-Dihydro-3-[(L)-norleucynyl]-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride

Through a solution of the product from Step A (1.35 g, 3.47 mmol) in 1,4-dioxane (200 mL) was passed a stream of HCl gas for 5 minutes. The reaction flask was capped and the solution stirred overnight at ambient temperature. The solution was concentrated to give 480 mg (41 %) of the title intermediate as a white solid, m.p 190 -196°C.

Physical data were as follows:

C<sub>16</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>Cl (MW 338.837), mass spectroscopy, MH<sup>+</sup> 303.2 (minus HCl).

Analytical for C<sub>16</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>Cl 0.5H<sub>2</sub>O: Theory, C, 55.24; H, 6.95; N, 16.10. Found, C, 55.12; H, 6.60; N, 15.59.

Exact Mass. For C<sub>16</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>: Theory 303.1821, Found 303.1803.

Example 48

**Synthesis of  
1,3,4,5-Tetrahydro-3-[(L)-norleucynyl]-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride**



Step A - Synthesis of 1,3,4,5-Tetrahydro-3-[N'-(*t*-butoxycarbonyl)-L-norleuciny]-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one

5 To a solution of the product from Example 45 (1.62 g, 6.92 mmol) in THF (120 mL) was added (L)-Boc-Nva-OH (1.65 g, 7.60 mmol, Bachem), HOBT (1.03 g, 7.60 mmol), EDC (1.46 g, 7.6 mmol), N,N-diisopropylethylamine (1.32 mL, 7.6 mmol). The resulting mixture was stirred at ambient temperature overnight. The mixture was diluted with EtOAc (200  
10 mL) and washed with H<sub>2</sub>O (200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexanes/EtOAc (6:4) afforded 1.74 g (58%) of the title intermediate as a white solid, m.p. 186-187°C.

Physical data were as follows:

C<sub>23</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub> (MW 432.561), mass spectroscopy, MH<sup>+</sup> 433.4, MH<sup>-</sup> 431.4  
15 Exact Mass. Calcd. for C<sub>23</sub>H<sub>37</sub>N<sub>4</sub>O<sub>4</sub>: Theory 433.2817, Found 433.2815.

20 Step B - Synthesis of 1,3,4,5-Tetrahydro-3-[(L)-norleuciny]-amino-1-methyl-4-isopropyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride

Through a solution of the product from Step A (1.78 g, 4.1 mmol) in 1,4-dioxane (200 mL) was passed a stream of HCl gas for 5 minutes. The reaction flask was capped and the solution stirred overnight at ambient temperature. The  
25 solution was concentrated to give 1.43 g (95 %) of the title intermediate as a white solid, m.p. 200-210°C.

Physical data were as follows:

C<sub>18</sub>H<sub>29</sub>N<sub>4</sub>O<sub>2</sub>Cl (MW 368.906), mass spectroscopy, MH<sup>+</sup> 334.3 (minus HCl), MH<sup>-</sup> 333.2.(minus HCl).  
30 Exact Mass. Calcd. for C<sub>18</sub>H<sub>29</sub>N<sub>4</sub>O<sub>2</sub>: Theory 333.2290, Found 333.2272.

Example 49

Synthesis of

**1,3-Dihydro-3-(L-norleucinyl)-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride**

5           Step A -       Synthesis of 1,3-Dihydro-3-[N'-(*t*-butoxycarbonyl)-L-norleucinyl]-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one

To a solution of the product from Example 39, Step E (2.35 g, 8.85 mmol) in THF (160mL) was added (L)-Boc-Nva-OH (2.11 g, 9.73 mmol), HOBT (1.31 g, 9.73 mmol), EDC (1.86 g, 9.73 mmol), and N,N-diisopropylethylamine (1.70 mL, 9.73 mmol). The resulting mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with EtOAc (480 mL), then washed with H<sub>2</sub>O (160 mL), saturated NaHCO<sub>3</sub> (160 mL), and brine (160 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. HPLC purification eluting with hexane/EtOAc (8:2 to 1:1) afforded 2.04 g of the title intermediate as a yellow foam (50 % yield), m.p. 102-105°C.

Physical data were as follows:

Exact Mass, Calc. For C<sub>25</sub>H<sub>33</sub>N<sub>4</sub>O<sub>4</sub>: 465.2502, found: 465.2502.

20           Step B -       Synthesis of 1,3-Dihydro-3-(L-norleucinyl)-amino-1-methyl-4-phenyl-(2H)-1,5-benzodiazepin-2-one Hydrochloride

Through a solution of the product from Step A (2.04 g, 4.39 mmol) in 1,4-dioxane (100 mL ) was passed a stream of HCl gas for 15 minutes at 0°C. The reaction flask was capped and the solution stirred overnight at ambient temperature. The solution was concentrated to give 1.83 g of the title intermediate as a yellow solid, m.p. 184-187°C.

Physical data were as follows:

Exact Mass. Calc. For C<sub>21</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>: 365.1977, found: 365.1968.

30

**Example 50**

**Synthesis of  
3-Amino-1-methyl-5-phenyl-  
1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one**

Step A - Synthesis of 5-Phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one (CAS. No. 32900-17-7)

Following the procedure described in WO 96/40653, PCT US 96/08331, Step 1-A using N-phenyl-1,2-phenylenediamine (Aldrich) and methyl acrylate (Aldrich), the title intermediate was prepared.

Physical data was as follows:

$C_{15}H_{14}N_2O$  (MW 238.29), Mass spectroscopy,  $MH^+$  239.2.

Anal. Calcd. for  $C_{15}H_{14}N_2O$ : C, 75.61; H, 5.92; N, 11.76. Found C, 75.88; H, 5.94; N, 11.69.

Step B - Synthesis of 1-Methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Following the General Procedure J using the product from Step A and methyl iodide (Aldrich), the title intermediate was prepared. HPLC purification eluting with EtOAc/hexanes (1:1) afforded the title intermediate as a light pink solid.

Physical data were as follows:

$C_{16}H_{16}N_2O$  (MW 252.32), Mass spectroscopy,  $MH^+$  253.2

Anal. Calcd. for  $C_{16}H_{16}N_2O$ : C, 76.16; H, 6.39; N, 11.10. Found C, 76.00; H, 6.19; N, 11.13.

Step C - Synthesis of 3-Azido-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Following the General Procedure H using the product from Step B, the title intermediate was prepared. HPLC purification eluting with hexane/EtOAc (6:4) afforded a the title intermediate as a thick yellow oil.

Physical data were as follows:

$C_{16}H_{15}N_3O$  (MW 293.33), Mass spectroscopy,  $MH^+$  294.2.

Step D - Synthesis of 3-Amino 1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Following General Procedure I using the product from Step C, the title intermediate was prepared. The title intermediate was prepared as a thick yellow oil and used without further purification.

Physical data were as follows:

5  $C_{16}H_{17}N_3O$  (MW 267.33), Mass spectroscopy,  $MH^+$  268.4

#### Example 51

##### Synthesis of

10 **3-(N'-L-Alaninyl)amino-1-methyl-5-phenyl-  
1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one**

Step A - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

15 Following General Procedure D with the product from Example 50, Step D and Boc-L-alanine (Nova Biochem), the title intermediate was prepared. HPLC purification eluting with  $CH_2Cl_2/MeOH$  (97:3 ) afforded the title intermediate as an amorphous white solid.

Physical data were as follows:

20  $C_{24}H_{30}N_4O_4$  (MW 438.52), Mass spectroscopy,  $MH^+$  439.2,  $MH^-$  437.4.  
Anal. Calcd. for  $C_{24}H_{30}N_4O_4$ : C, 65.73; H, 6.90; N, 12.78. Found C, 65.70; H, 6.65; N, 12.48.

25 Step B - Synthesis of 3-(L-Alaninyl)-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Following General Procedure E using the product from Step A, the title intermediate was prepared. HPLC purification eluting with  $CH_2Cl_2/MeOH$  (95:5) afforded the title intermediate as a mixture of diastereomers. A second HPLC purification eluting with  $CH_2Cl_2/MeOH$  (99:1 gradient, raising the MeOH concentration by 1% every 10 minutes) afforded the separated diastereomers (isomer A and isomer B) as pale yellow solids.

Physical data were as follows:

First eluting isomer (isomer A):

$C_{19}H_{22}N_4O_2$  (MW 338.41), mass spectroscopy, 338.4.

Second eluting isomer (isomer B):

$C_{19}H_{22}N_4O_2$  (MW 338.41), mass spectroscopy,  $MH^+$  339.0.

5

## Example 52

### Synthesis of 3-(L-Valinyl)-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5- benzodiazepin-2-one

10

Step A - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-valinyl]-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one

15

Following General Procedure D using the product from Example 50 and Boc-L-valine (Nova Biochem), the title intermediate was prepared. HPLC purification eluting with hexanes/EtOAc (7:3) afforded the title intermediate as a white solid.

Physical data were as follows:

20

$C_{26}H_{34}N_4O_4$  (MW 466.58). mass spectroscopy,  $MH^+$  467.4,  $MH^-$  465.3.

Anal calcd. for  $C_{26}H_{34}N_4O_4$ : Theory, C, 66.93; H, 7.35; N, 12.01.

Found, C, 66.79; H, 7.14; N, 11.76.

25

Step B - Synthesis of 3-(L-Valinyl)-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one

Following the General Procedure E using the product from Step A, the title compound was prepared. HPLC purification eluting with  $CH_2Cl_2$ /MeOH (95:5), and a second HPLC purification eluting with (99:1), afforded the individual isomers A (first eluting) and B (second eluting) of the title compound.

30

Physical data were as follows:

$C_{21}H_{26}N_4O_2$  (MW 366.46). mass spectroscopy  $MH^+$  367.2 (similar for both isomers).

First eluting isomer (A):

Anal calcd. for  $C_{21}H_{26}N_4O_2$ : Theory, C, 68.83; H, 7.15; N, 15.29.

Found, C, 68.68; H, 7.06; N, 15.17.

Specific rotation in MeOH, 1mL cell, 0.5% C at 589 = +85.01°.

Second eluting isomer (B):

5            Exact mass anal calcd. for  $C_{21}H_{27}N_4O_2$ : Theory 367.2134. Found, 367.2120.

Specific rotation in MeOH, 1mL cell, 0.5% C at 589 = - 17.52°.

### Example 53

10

#### Synthesis of

#### **3-[L-(O-Benzyl)-threoninyl]-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one**

15

Step A -        Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-(O-benzyl)-threoninyl]-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one

20

Following General Procedure K using the product from Example 50 and Boc-O-benzyl-L-threonine (Sigma), the title intermediate was prepared. HPLC purification eluting with hexanes/EtOAc (4:1 to 3:1 gradient) afforded separation of the individual isomers, A and B, of the title intermediate.

25

Step B -        Synthesis of 3-[L-(O-Benzyl)-threoninyl]-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepin-2-one

Following General Procedure E using the individual isomers, A and B, from Step A, the title compound was prepared.

Physical data were as follows:

30

$C_{27}H_{30}N_4O_3$  (MW 458.56), mass spectroscopy,  $MH^+$  459.6,  $MH^-$  457.5 (similar for both isomers).

Product from isomer A:

Specific rotation in MeOH, 1mL cell, 0.5% C at 589 = -173.72°.

Product from isomer B:

Specific rotation in MeOH, 1mL cell, 0.5% C at 589 = +91.22°.

Example 54

Synthesis of

5 3-(S)-Phenylglycinyll]-amino-  
5-phenyl-1-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Step A - Synthesis of 3-[N'-(t-Butoxycarbonyl)-(S)-phenylglycinyll]-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine 2-one

10 Following modified General Procedure L using the product from Example 50 and Boc-L-Phenylglycine (Nova Biochem), the title intermediate was prepared. The modification was that the reaction was only stirred for 6 hours. HPLC purification eluting with 80/20 hexanes/EtOAc afforded the separated diastereomers; isomer 1 (first eluting) and isomer 2 (second eluting).

15 Physical data were as follows:

$C_{29}H_{32}N_4O_4$  (MW 500.60); mass spectroscopy for isomer 1:  $MH^+$  501.2;  $MH^+$ , 499.3; mass spectroscopy for isomer 2:  $MH^+$  501.2;  $MH^+$ , 499.3.

20 Step B - Synthesis of 3-((S)-Phenylglycinyll)-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine 2-one

Following the General Procedure E using the products (Isomers 1 and 2 brought through reaction sequence separately) from Step A, the title intermediates were prepared. HPLC purification eluting with 95/5 methylene chloride/methanol afforded the title intermediates as a light yellow oils.

25 Physical data were as follows:

$C_{24}H_{24}N_4O_2$  (MW 400.48); mass spectroscopy for isomer 1:  $MH^+$ , 401.3;  $MH^+$ , 399.2; mass spectroscopy for isomer 2:  $MH^+$ , 401.2;  $MH^+$ , 399.3.

Example 55

Synthesis of

30 3-Amino-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Step A - Synthesis of N,N'-Dimethyl-1,2-phenylenediamine (CAS No. 3213-79-4)

Following the literature procedures of H. Stetter, *Chem. Ber.*, **1953**, 86, 161 and G. W. H. Cheeseman, *J. Chem. Soc.*, **1955**, 3308, the title intermediate was prepared from 1,2-phenylenediamine (Aldrich) as a low melting solid.

Physical data was as follows:

5  $C_8H_{12}N_2$  (MW 136); mass spectroscopy, 136.1.

Exact mass anal. Calcd. for  $C_8H_{13}N_2$ : Theory, 137.1079, Found, 137.081

Step B - Synthesis of 1,5-Bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzadiazepine-2-one

10 To a solution of the product from Step A (400 mg, 2.94 mmols) in 5M Aq. HCl (30 mL) was added acrylic acid (0.202 mL, 3.23 mmols, Aldrich) and the mixture heated to reflux for 18 hours. The black mixture was allowed to cool, then poured onto ice and the pH adjusted to 10 with 5M Aq. NaOH. The product was extracted into  $CH_2Cl_2$  (200 mL) and washed with water (100 mL) and brine (100  
15 mL). The organic phase was dried over  $Na_2SO_4$ , filtered, and concentrated to give a black oil. HPLC purification eluting with hexanes/EtOAc (1:1) afforded 364 mg of the title intermediate as a brown oil.

Physical data were as follows:

$C_{11}H_{14}N_2O$  (MW 190.25); mass spectroscopy,  $MH^+$  191.4.

20 Anal. Calcd. for  $C_{11}H_{14}N_2O$ : Theory, C, 69.45; H, 7.42; N, 14.72; Found, C, 69.26; H, 7.40; N, 14.64.

Step C - Synthesis of 3-Azido-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzadiazepine-2-one

25 Following General Procedure H using the product from Step B, the title intermediate was prepared. HPLC purification eluting with hexanes/EtOAc (7:3) afforded the title intermediate as a light brown oil.

Physical data were as follows:

$C_{11}H_{13}N_5O$  (MW 231.26), mass spectroscopy,  $MH^+$  232.2

30 Exact mass Anal. Calcd. for  $C_{11}H_{14}N_5O$ : Theory, 232.1198; Found, 232.1196.



Step D - Synthesis of 3-Amino-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Following General Procedure I using the product from Step C, the title intermediate was prepared and used without chromatographic purification.

5 Physical data were as follows:

$C_{11}H_{15}N_3O$  (MW 205.26), mass spectroscopy  $MH^+$  206.2.

Exact mass Anal. Calcd. for  $C_{11}H_{16}N_3O$ : Theory, 206.1293; Found, 206.1295.

10

Example 56

**Synthesis of  
3-(L-Alaninyl)-amino-  
1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one**

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Step A - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Following General Procedure D using the product from Example 55 and Boc-L-alanine (Nova Biochem), the title intermediate was prepared. HPLC purification eluting with EtOAc/hexanes (6:4) afforded the title intermediate as a white foamy solid.

20

Physical data were as follows:

$C_{19}H_{28}N_4O_4$  (MW 376.45), mass spectroscopy  $MH^+$ , 377.4,  $MH^-$ , 375.3.

Anal. Calcd. for  $C_{19}H_{28}N_4O_4$ : Theory, C, 60.62; H, 7.50; N, 14.88. Found,

25

C, 60.68; H, 7.42; N, 14.38.

Step B - Synthesis of 3-(L-Alaninyl)-amino-1,5-bis-methyl-1,3,4,5-tetrahydro-(2H)-1,5-benzodiazepine-2-one

Following the General Procedure E using the product from Step A, the title compound was prepared. HPLC purification eluting with EtOAc/hexanes (6:4) afforded the title compound as a thick yellow oil.

30

Physical data were as follows:

$C_{14}H_{20}N_4O_2$ : (MW 276.34), mass spectroscopy,  $MH^+$ , 277.2.

The following examples illustrate how a compound prepared from a synthetic intermediate of this invention could be assayed to determine its ability to inhibit  $\beta$ -amyloid production in a cell or tested to determine its ability to suppress  $\beta$ -amyloid release and/or synthesis *in vivo*.

5

#### Example 57

##### Cellular Screen for the Detection of Inhibitors of $\beta$ -Amyloid Production

Using the procedure of this example, compounds can be assayed for their ability to inhibit  $\beta$ -amyloid production in a cell line possessing the Swedish mutation. This screening assay employs cells (K293 = human kidney cell line) which are stably transfected with the gene for amyloid precursor protein 751 (APP751) containing the double mutation Lys<sub>651</sub>Met<sub>652</sub> to Asn<sub>651</sub>Leu<sub>652</sub> (APP751 numbering) in the manner described in International Patent Application Publication No. 94/10569<sup>15</sup> and Citron et al.<sup>16</sup>. This mutation is commonly called the Swedish mutation and the cells, designated as "293 751 SWE", are plated in Corning 96-well plates at  $2-4 \times 10^4$  cells per well in Dulbecco's minimal essential media (Sigma, St. Louis, MO) plus 10% fetal bovine serum. Cell number is important in order to achieve  $\beta$ -amyloid ELISA results within the linear range of the assay ( $\sim 0.2$  to  $2.5$  ng per mL).

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15  
20

Following overnight incubation at  $37^\circ\text{C}$  in an incubator equilibrated with 10% carbon dioxide, media are removed and replaced with  $200\ \mu\text{L}$  of a compound to be tested (drug) containing media per well for a two hour pretreatment period and cells are incubated as above. Drug stocks are prepared in 100% dimethyl sulfoxide such that at the final drug concentration used in the treatment, the concentration of dimethyl sulfoxide does not exceed 0.5% and, in fact, usually equals 0.1%.

25

At the end of the pretreatment period, the media are again removed and replaced with fresh drug containing media as above and cells are incubated for an

30

additional two hours. After treatment, plates are centrifuged in a Beckman GPR at 1200 rpm for five minutes at room temperature to pellet cellular debris from the conditioned media. From each well, 100  $\mu$ L of conditioned media or appropriate dilutions thereof are transferred into an ELISA plate precoated with antibody 266 [P. Seubert, *Nature* (1992) **359**:325-327<sup>17</sup>] against amino acids 13-28 of  $\beta$ -amyloid peptide as described in International Patent Application Publication No. 94/10569<sup>15</sup> and stored at 4°C overnight. An ELISA assay employing labeled antibody 3D6 [P. Seubert, *Nature* (1992) **359**:325-327<sup>17</sup>] against amino acids 1-5 of  $\beta$ -amyloid peptide is run the next day to measure the amount of  $\beta$ -amyloid peptide produced.

Cytotoxic effects of the compounds are measured by a modification of the method of Hansen, et al.<sup>18</sup>. To the cells remaining in the tissue culture plate is added 25  $\mu$ L of a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, St. Louis, MO) stock solution (5 mg/mL) to a final concentration of 1 mg/mL. Cells are incubated at 37°C for one hour, and cellular activity is stopped by the addition of an equal volume of MTT lysis buffer (20% w/v sodium dodecylsulfate in 50% dimethylformamide, pH 4.7). Complete extraction is achieved by overnight shaking at room temperature. The difference in the OD<sub>562nm</sub> and the OD<sub>650nm</sub> is measured in a Molecular Device's UV<sub>max</sub> microplate reader as an indicator of the cellular viability.

The results of the  $\beta$ -amyloid peptide ELISA are fit to a standard curve and expressed as ng/mL  $\beta$ -amyloid peptide. In order to normalize for cytotoxicity, these results are divided by the MTT results and expressed as a percentage of the results from a drug free control. All results are the mean and standard deviation of at least six replicate assays.

The test compounds are assayed for  $\beta$ -amyloid peptide production inhibition activity in cells using this assay. The results of this assay can be used

to demonstrate that the compounds prepared from the intermediates of this invention inhibit  $\beta$ -amyloid peptide production by at least 30% as compared to control when employed at 10  $\mu$ g/mL.

5

#### Example 58

##### ***In Vivo* Suppression of $\beta$ -Amyloid Release and/or Synthesis**

This example illustrates how the compounds prepared from the intermediate compounds of this invention could be tested for *in vivo* suppression of  $\beta$ -amyloid release and/or synthesis. For these experiments, 3 to 4 month old PDAPP mice are used [Games et al., (1995) *Nature* 373:523-527<sup>19</sup>]. Depending upon which compound is being tested, the compound is usually formulated at between 1 and 10 mg/mL. Because of the low solubility factors of the compounds, they may be formulated with various vehicles, such as corn oil (Safeway, South San Francisco, CA); 10% ethanol in corn oil; 2-hydroxypropyl- $\beta$ -cyclodextrin (Research Biochemicals International, Natick MA); and carboxy-methyl-cellulose (Sigma Chemical Co., St. Louis MO).

10  
15

The mice are dosed subcutaneously with a 26 gauge needle and 3 hours later the animals are euthanized via CO<sub>2</sub> narcosis and blood is taken by cardiac puncture using a 1 cc 25G 5/8" tuberculin syringe/needle coated with solution of 0.5 M EDTA, pH 8.0. The blood is placed in a Becton-Dickinson vacutainer tube containing EDTA and spun down for 15 minutes at 1500 xg at 5°C. The brains of the mice are then removed and the cortex and hippocampus are dissected out and placed on ice.

20

25

##### 1. Brain Assay

To prepare hippocampal and cortical tissue for enzyme-linked immunosorbent assays (ELISAs) each brain region is homogenized in 10 volumes of ice cold guanidine buffer (5.0 M guanidine-HCl, 50 mM Tris-HCl, pH 8.0) using a Kontes motorized pestle (Fisher, Pittsburgh PA). The homogenates are

30

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gently rocked on a rotating platform for three to four hours at room temperature and stored at -20°C prior to quantitation of  $\beta$ -amyloid.

The brain homogenates are diluted 1:10 with ice-cold casein buffer  
5 [0.25% casein, phosphate buffered saline (PBS), 0.05% sodium azide, 20  $\mu$ g/mL aprotinin, 5 mM EDTA, pH 8.0, 10  $\mu$ g/mL leupeptin], thereby reducing the final concentration of guanidine to 0.5 M, before centrifugation at 16,000 xg for 20 minutes at 4°C. Samples are further diluted, if necessary, to achieve an optimal range for the ELISA measurements by the addition of casein buffer with 0.5 M  
10 guanidine hydrochloride added. The  $\beta$ -amyloid standards (1-40 or 1-42 amino acids) were prepared such that the final composition equaled 0.5 M guanidine in the presence of 0.1% bovine serum albumin (BSA).

The total  $\beta$ -amyloid sandwich ELISA, quantitating both  $\beta$ -amyloid (aa 1-  
15 40) and  $\beta$ -amyloid (aa 1-42) consists of two monoclonal antibodies (mAb) to  $\beta$ -amyloid. The capture antibody, 266 [P. Seubert, *Nature* (1992) 359:325-327<sup>17</sup>], is specific to amino acids 13 - 28 of  $\beta$ -amyloid. The antibody 3D6 [Johnson-Wood et al., *PNAS USA* (1997) 94:1550-1555<sup>20</sup>], which is specific to amino acids 1 - 5 of  $\beta$ -amyloid, is biotinylated and served as the reporter antibody in the  
20 assay. The 3D6 biotinylation procedure employs the manufacturer's (Pierce, Rockford IL) protocol for NHS-biotin labeling of immunoglobulins except that 100 mM sodium bicarbonate, pH 8.5 buffer is used. The 3D6 antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP but detects only  $\beta$ -amyloid species with an amino terminal aspartic acid. The assay  
25 has a lower limit of sensitivity of  $\sim$  50 pg/mL (11 pM) and shows no cross-reactivity to the endogenous murine  $\beta$ -amyloid peptide at concentrations up to 1 ng/mL.

The configuration of the sandwich ELISA quantitating the level of  $\beta$ -  
30 amyloid (aa 1-42) employs the mAb 21F12 [Johnson-Wood et al., *PNAS USA*

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(1997) 94:1550-1555<sup>20]</sup> (which recognizes amino acids 33-42 of  $\beta$ -amyloid) as the capture antibody. Biotinylated 3D6 is also the reporter antibody in this assay which has a lower limit of sensitivity of  $\sim 125$  pg/mL (28 pM).

5           The 266 and 21F12 capture mAbs are coated at 10  $\mu$ g/mL into 96 well immunoassay plates (Costar, Cambridge MA) overnight at room temperature. The plates are then aspirated and blocked with 0.25% human serum albumin in PBS buffer for at least 1 hour at room temperature, then stored desiccated at 4°C until use. The plates are rehydrated with wash buffer (Tris-buffered saline,  
10   0.05% Tween 20) prior to use. The samples and standards are added to the plates and incubated overnight at 4°C. The plates are washed  $\geq 3$  times with wash buffer between each step of the assay. The biotinylated 3D6, diluted to 0.5  $\mu$ g/mL in casein incubation buffer (0.25% casein, PBS, 0.05% Tween 20, pH 7.4) is incubated in the well for 1 hour at room temperature. Avidin-HRP  
15   (Vector, Burlingame CA) diluted 1:4000 in casein incubation buffer is added to the wells for 1 hour at room temperature. The colorimetric substrate, Slow TMB-ELISA (Pierce, Cambridge MA), is added and allowed to react for 15 minutes, after which the enzymatic reaction is stopped with addition of 2 N H<sub>2</sub>SO<sub>4</sub>. Reaction product is quantified using a Molecular Devices Vmax  
20   (Molecular Devices, Menlo Park CA) measuring the difference in absorbance at 450 nm and 650 nm.

## 2.    Blood Assay

25           The EDTA plasma is diluted 1:1 in specimen diluent (0.2 gm/l sodium phosphate•H<sub>2</sub>O (monobasic), 2.16 gm/l sodium phosphate•7H<sub>2</sub>O (dibasic), 0.5gm/l thimerosal, 8.5 gm/l sodium chloride, 0.5 mL Triton X-405, 6.0 g/l globulin-free bovine serum albumin; and water). The samples and standards in specimen diluent are assayed using the total  $\beta$ -amyloid assay (266 capture/3D6 reporter) described above for the brain assay except the specimen diluent was  
30   used instead of the casein diluents described.

Formulations other than those described above can also be used for oral delivery and intravenous delivery to a mammal. For oral delivery, the compound can be mixed with either 100% corn oil or, alternatively, in a solution containing 80% corn oil, 19.5% oleic acid and 0.5% labrafil. The compound can be mixed  
5 with the above solutions in concentrations ranging from 1 mg/mL to 10 mg/mL. The compound in solution is preferably administered orally to the mammal at a dose volume of 5 mL/kg of body weight. For IV delivery, the compound is preferably mixed with a solution of 3% ethanol, 3% solutol HS-15 and 94% saline. The compound is preferably mixed with the above solution in  
10 concentrations ranging from 0.25 mg/mL to 5 mg/mL. The compound in solution is preferably administered by IV to the mammal at a dose volume of 2 mL/kg of body weight.

From the foregoing description, various modifications and changes in the  
15 composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

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